CANCER OF THE LUNG

Pathology, Diagnosis, and Treatment

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'Men at some time are masters of their fates·
The fault, dear Brutus, is not in our stars,
But in ourselves .'

JULIUS CAESAR, Act I, Scene 2

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Foreword

The passing years have witnessed tremendous changes in our attitude toward cancer of the lung The orbit of interest has steadily widened to include the pathologist, clinician, radiologist, and surgeon Two decades have passed since the first successful resection for bronchogenic carcinoma, but despite the progress in surgical technique, the number of cured patients remains very small It is apparent that a much wider dissemination of knowledge is necessary before the over-all picture can be significantly improved

It has been repeatedly demonstrated that cancer of the lung can be successfully resected if detected in a noninvasive state The diagnostic criteria of the past have been expressions of far-advanced disease and not of early lesions The detection of resectable lung cancer depends primarily on the development of a high index of suspicion by the clinician and the radiologist The readily diagnosed case is usually inoperable. Too many patients have passed through silent phases of the disease to reach a metastatic stage under the aegis of watchful waiting

The material presented in this monograph was derived chiefly from the medical wards of the New York City Hospital, and from private practice Correlation between clinical and pathological findings has been stressed throughout to provide a more basic understanding to the problem of early diagnosis The illustrative cases were selected on the basis of instructive value rather than on rarity of occurrence

Progress in surgery has resolved the issue to one of detection of the noninvasive lesion This will be achieved only by re-evaluation of the clinical and roentgen manifestations in the light of our present knowledge of pathogenesis To this objective, this volume is dedicated

The authors are greatly indebted to the distinguished contributors who made this comprehensive study possible All practitioners of medicine will profit from the chapters dealing with the various aspects of lung cancer In addition, specialists in the respective fields will find many useful technical suggestions in the chapters, Exfoliative Cytology by Papanicolaou and Foot, Surgical Therapy by Chamberlain and Daniels, Bronchoscopy by Jackson, and Palliative Treatment by Roswit

The co-operation of many colleagues in making available their illustrative material is also gratefully acknowledged. A final word of thanks goes to the editorial staff of the Oxford University Press for many helpful suggestions, to the Keturah Blakely Studio for painstaking reproductions, to Julia Spruch, Charles Freeman, and Kermuth Cioppa for typing and arrangement of data, and to Mollie R. Rosenblatt for her multitudinous tasks in facilitating the completion of the manuscript.

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CANCER OF THE LUNG

I

Introductory Considerations

Cancer of the lung is at present the major problem in the field of pulmonary diseases Formerly considered a rarity in clinical medicine, it now ranks with cancer of the stomach. The recent decades have witnessed a tremendous rise in incidence Since 1930, the deaths from bronchogenic carcinoma have increased 500 per cent Whether this increase is relative or absolute is of secondary importance in view of the primary issue, which is therapy In order to cope with this problem effectively it is necessary to have a better understanding of the clinical and pathological manifestations The diagnosis of bronchogenic carcinoma is readily made in every modern hospital, but too often it is established when the disease is already far advanced

We have at our disposal today technical procedures which insure a high degree of accuracy in the recognition of this condition What we lack, primarily, is the clinical acumen to apply these techniques when the disease is in its incipiency. Our medical heritage has taught us to look for certain classic manifestations before instituting diagnostic or therapeutic measures Only recently have we realized that many of the symptoms and signs for which we have diligently searched represent metastatic or pre-terminal stages

Operability and Resectability

One of the best indices of accuracy in the early diagnosis of bronchogenic carcinoma is the ratio between the operable cases and the total number diagnosed A review of almost 15,000 cases (Table 1) reveals that less than 35 per cent were considered operable after adequate study This figure is of considerable significance when it is realized that the contraindications to surgery in pulmonary malignancy are relatively few Factors such as age, cardiovascular status, and general condition do not influence the decision to operate as they do in cases of bronchiectasis or tuberculosis The vast majority of patients with bronchogenic carcinoma are in the sixth and seventh decades of life and are expected to have varying degrees of degenerative changes.

TABLE I *Incidence of Operability and Resection*

AUTHOR	YEARS	TOTAL CASES	OPERATED CASES	RESECTED CASES
Bjork, V O	1937–1944	996	152 (15 3%)	75 (7 5%)
Hollingsworth, R. K	1938–1944	343	77 (22 5%)	43 (12.5%)
Adams, R	1930–1944	157	94 (60%)	49 (31 2%)
Graham, E A	1943–1945	221	112 (50.7%)	39 (18%)
Lambert, A	1939–1946	349	70 (20%)	25 (7.2%)
Edwards, A T	?–1946	1,016	173 (17%)	70 (7%)
Ariel, I M, Avery, E E, Kanter, L, Head, J R, and Langston, H T	1937–1947	1,057	141 (13.4%)	49 (4.6%)
Overholt, R. H and Schmidt, I C	1932–1948	604	289 (47 8%)	162 (26.8%)
McDonald, R, Carlisle, J, and Patton, M	1934–1948	856	415 (48 4%)	251 (29.3%)
Aufses, A	1935–1948	959	330 (34 4%)	165 (17.2%)
Mason, G A	1933–1948	1,000	353 (35%)	202 (20%)
Brock, R C.	1941–1948	800	172 (21.5%)	106 (13 2%)
Brooks, W D, Davidson, M, Thomas, C, Robson, D, and Smithers, D	1944–1949	502	53 (10 5%)	20 (4%)
Moore, R L	1940–1949	370	157 (42%)	88 (24%)
Bloomer, W E and Lindskog, G E	1938–1949	300	120 (40%)	64 (21 3%)
Paulson, D and Shaw, R	1937–1950	362	182 (50%)	107 (30%)
Churchill, E D, Sweet, R H, Soutter, L, and Scannell, J G	1930–1950	1,130	294 (26%)	171 (15%)
Ochsner, A, DeCamp, P, DeBakey, M, and Ray, C	1935–1951	948	512 (54%)	332 (35%)
Boyce, F.	1947–1951	750	289 (37 2%)	125 (16 6%)
Jones, J	1942–1952	663	288 (45 5%)	149 (23 5%)
Brea, M	1944–1952	880	311 (35 3%)	200 (22.7%)
Gibbon, J, Allbritten, R, Templeton, J, III, and Nealon, T, Jr	1946–1953	532	380 (71.5%)	205 (38.5%)

Total Number of Cases	14 795
Total Cases Operated	4,964 (33 6%)
Total Cases Resected	2,697 (18 2%)

The chief contraindication to surgery in cancer of the lung is metastatic extension of the tumor. The exclusion of 65 per cent of the cases from the operable category strongly suggests that they had obvious metastatic foci at the time the diagnosis was made In the group that was considered operable and subjected to thoracotomy, approximately half the cases showed metastatic foci on exploration In only 18 per cent of the total group was resection performed It would appear, therefore, on the basis of these statistics that only one patient out of five is diagnosed sufficiently early to permit definitive surgical therapy

The over-all picture in regard to early diagnosis is even more appalling It is impossible to obtain a completely accurate evaluation of the situation and the statistical data at our disposal is largely selective. It represents, to a high degree, patients who were considered operable cases by their own physicians and were referred to large medical centers for treatment. If in

this selected group the rate of resectability is only 18 per cent, it is evident that the rate for all diagnosed cases must be piteously low.

Comparative Studies

Despite the progress of recent years, there can be no radical revision of the statistics until there is a drastic change in the concept of early diagnosis The recognition of greater numbers of cases each year has not brought with it a corresponding increase in the number of operable cases According to the National Office of Vital Statistics there were 2,837 deaths from carcinoma of the lung in 1930 and 18,313 deaths in 1950. This increase of 500 per cent bears good witness of the improved ability to diagnose the disease, but the small number of surgically acceptable cases proves that our skill is limited for the most part to far-advanced cases.

The statistics from the University of Michigan Hospital are of interest in this connection In the period 1933–8 there were 137 cases of bronchogenic carcinoma diagnosed out of a total hospital registration of 152,150 In the period 1938–44 there were 343 cases out of a total hospital registration of 177,005 The relative increase in lung cancer cases was far greater than the increase in the total registration and indicates greater diagnostic skill and intensified interest in the disease However, the vast majority of cases diagnosed in the latter period were of a far-advanced status. Only 77 patients (22 per cent) were considered operable and only 43 patients (12 5 per cent) were found resectable.

Even the best of the available reports leave much to be desired In Ochsner's series of 948 cases the rate of operability was 59 per cent and the rate of resection was 35 per cent There were 51 patients considered operable who declined surgery If this group had consented the results would probably have been even more favorable Adams reported an operability rate of 60 per cent and a resectability rate of 31 per cent In a series of 234 cases observed by Overholt between 1932 and 1943 there were 99 operable cases (42 per cent) of which 41 (18 per cent) were resected Between 1943 and 1949 there were 487 cases added to the series, making a total of 721 cases Thoracotomy was performed in 342 cases (47 per cent) and resection was possible in 200 cases (28 per cent) These figures show a significant improvement over the general picture but still stand as an indictment of inability to diagnose non-metastatic cases

In general, the hope that the improved methods of diagnosis used in recent years would result in the recognition of a large number of early cases has not been realized Even the statistical increase in the number of resectable cases is often misleading An increased resectability rate should signify diagnosis of a greater number of early cases, but may actually be due to greater surgical ingenuity and courage in tackling the far-advanced case. In Over-

holt's series of 721 patients only 9 per cent presented themselves for treatment when the tumor was still confined to the lung.

Comparison of two consecutive equal series of cases reported by Lindskog and Bloomer provides an index of progress in early diagnosis The first series of 100 cases of bronchogenic carcinoma was observed during a five-year period ending December 1943, the second series from January 1944 through the succeeding three and a half years. In series I 65 per cent of the cases were inoperable and in series II, 57 per cent. There were 32 explorations with 12 resections in series I and 40 explorations with 20 resections in series II. While the resectability rate increased considerably in the second series this did not indicate an increase in early diagnosed cases. Of the 21 resections, only 11 were done on patients with the disease confined to the lung of origin In the other 10 cases there were obvious metastases seen at operation and surgery was only palliative

The experience of Churchill at the Massachusetts General Hospital also affirms the lack of progress in the detection of resectable lesions. In a series *of 155 cases reported in 1940 there were 52 (33 6 per cent) patients found* suitable for surgery, of which 27 (17 4 per cent) could be resected. Ten years later the series had grown to 1,130 clinically diagnosed cases with pathological confirmation in 681 In only 294 (26 per cent) was surgery indicated and in 171 (15 per cent) resection was done. If considerations are limited to the cases with pathological confirmation, the operability rate rises to 43 per cent and the resectability rate to 25 per cent.

The similarity in resectability rates throughout the various medical centers here and abroad is most noteworthy. It is apparent that regardless of surgical skill, improvements in anesthesia, and detailed post-operative care, progress in the treatment of bronchogenic carcinoma depends primarily on the ability to diagnose the resectable case The vast discrepancy between the number of cases referred for surgery and the number in which resection can be performed indicates clearly that pre-operative determination of the resectable case has been most difficult

Therapeutic results in the treatment of lung cancer have uniformly emphasized the problem. Unless the material has been carefully selected, less than 20 per cent of the patients diagnosed will be suitable for definitive surgery Jewett was able to resect 18 (12 per cent) out of a total series of 150 cases. Reiss found 10 (14 per cent) resectable out of 70 cases Paulson and Shaw resected 107 (30 per cent) out of 362 cases, but half of the resections were only palliative Out of a series of 1,057 cases at a Veterans Administration Hospital, Ariel reported 141 (13 4 per cent) thoracotomies and 49 (4 6 per cent) resections Lambert resected 25 (7.2 per cent) out of 349 cases at the Bellevue Hospital

Mason reviewed 1,000 cases in England and Wales and found 202 (20 per cent) resectable At Johns Hopkins, Rienhoff operated on 502 patients and was able to resect 158 (31 per cent). However, 70 per cent of the resected

cases had metastases to the bronchial and tracheal nodes. In general, the results in later years have shown no great improvement over the earlier figures despite the progress in thoracic surgery and the greater number of skilled thoracic surgeons available.

Retrospective studies of bronchogenic carcinoma have revealed that there is a period in which the disease is not generally detected or even suspected This latent period, when carefully reviewed, is often found associated with clinical or roentgen findings which were unsuspected during observation of the case The problem of latency therefore lies not in the inherent characteristics of bronchogenic carcinoma, but in the general inability to recognize the disease in its early phases

Analogy with Tuberculosis

At this point a parallel may well be drawn between the establishment of diagnostic criteria in pulmonary tuberculosis and in pulmonary cancer Before the widespread use of the roentgen examination the student was taught to look for apical dullness and rales, altered breath sounds, retracted thoraces, and muscular atrophy as signs of incipient tuberculosis. Today it is generally recognized that these are usually the manifestations of far-advanced disease It took three decades of extensive surveys as well as hospital and private experience to demonstrate that the early lesion in tuberculosis is not only without symptoms but also without physical signs The diagnosis of minimal tuberculosis is usually a fortuitous one resulting from X-ray examination of contacts, mass surveys, pre-employment, and general check-ups When a presumptive diagnosis can be made on the basis of physical signs, the conditions have usually passed beyond the incipient stage

Delays in Diagnosis

In carcinoma, the necessity for early diagnosis is imperative It is still not generally recognized that the disease may remain silent for months or years, or that it may masquerade as pneumonitis, tuberculosis, bronchiectasis, abscess, or many other pulmonary disorders The clinician and even the roentgenologist have been too exacting in their diagnostic criteria, not fully realizing that the signs they were seeking were those of far-advanced disease

There are two outstanding reasons for the general failure in diagnosing early, or operable, bronchogenic carcinoma The first is the indifference of the patient to his own symptoms and his subsequent reluctance to seek medical advice. The second is the failure of the physician always to include cancer of the lung in his differential diagnosis of obscure pulmonary disorders Estimates of average delay between onset of symptoms and hospitalization have ranged from eight to twelve months with the attending physician usually credited with a considerable share in the procrastination

Once the diagnosis is established there is usually little delay in deciding on surgical intervention.

From the practical point of view *the fact that a patient has but recently* noted hemoptysis, cough, chest pain, or weight loss does not always imply that his disease is minimal. There is often little relation between the onset of definite pulmonary symptoms and the extent of the disease process In many instances the early symptoms are entirely non-pulmonary.

Sources of Early Lesions

Probably the most fruitful source of early malignant lesions is the routine examination that includes a chest film In this manner it is possible to diagnose nodular lesions that are entirely asymptomatic It has been shown that this type of cancer extends very slowly and is readily resectable when diagnosed early Cases have been reported in which the nodules have been observed for years under the erroneous impression that they were tuberculous in origin *Routine health surveys for tuberculosis, particularly those* that have included older age groups, have yielded many cases of unsuspected malignancy.

The crux of the problem, however, rests with the general practitioner, whether he is in his office or in the clinic or making ward rounds Unless he becomes aware of the early manifestations of bronchogenic carcinoma the ratio of operable to diagnosed cases will change little throughout the years. The role of the general practitioner is emphasized because he sees the greatest number of patients, sees them most often, and is responsible for consultations

The complete work-up of a suspected case of carcinoma may be accomplished within a few days in the average general hospital It has often been done within twenty-four hours. The presumptive diagnosis is established by the history, physical examination, X ray and hematological studies The diagnosis is confirmed by the bronchoscopic biopsy, examination of the sputum, examination of the pleural fluid, biopsy of an enlarged gland or subcutaneous mass, and roentgen evidence of metastases. Aspiration of the *tumor itself through the chest wall has been generally abandoned. All these* procedures are routine and are not the province of special institutions. The technical difficulties have been well mastered What is lacking is the application of these procedures at the right time

Typical Case Report

At a clinical-pathological conference held at a large teaching hospital there was presented a case of bronchogenic carcinoma The patient was a colored woman, about fifty years of age, who was hospitalized because of productive cough, dyspnea, and left chest pain On physical examination the intern elicited diminished fremitus, *dullness on percussion, and absent*

breath sounds on the left side of the chest The X ray showed a homogeneous opacity on the left side extending from the apex to the base The bronchoscopist found a mass in the left upper lobe bronchus, biopsy of which was positive for squamous cell carcinoma The clinical course was progressively downhill and metastatic lesions were suspected in the dorsal vertebrae and pelvis. The case was considered inoperable and the patient died one month after admission At necropsy the findings were precisely as suspected clinically.

During the discussion of the case the chairman asked if there were any alternate diagnoses and was promptly told that the diagnosis had been obvious from the start. Because of the high degree of correlation between the clinical and pathological findings the general atmosphere that prevailed approached that of omniscience Before the conference closed, however, it was brought to attention that the patient had previously attended the outpatient department and the following embarrassing facts were disclosed

1 The patient had attended the out-patient department for four years
2 Her initial complaint had been cough, dyspnea, and chest pain which had been ascribed to an associated hypertensive cardiovascular condition.
3 The patient had been fluoroscoped on numerous occasions in the cardiac clinic, and infiltrations in the left lung had been noted but attributed to vascular congestion
4 Recurrent episodes of low-grade fever were recorded in the clinic chart
5 The sedimentation rate was persistently elevated and six months before admission was 100 mm per hour There was also a persistent leukocytosis
6 The patient had complained of pains in the left chest, in the back, and in the hips, but these were considered of arthritic origin

In summarizing the clinic chart it was realized that the patient's symptoms of carcinoma had actually begun four years before her admission and that although she had been seen by a score of internists none had thought of a carcinoma work-up until the diagnosis had become obvious. This case in a way epitomizes the pulmonary cancer problem and emphasizes that what is lacking is not newer diagnostic techniques but the more frequent use of the ones we have.

The cry for early diagnosis would have little meaning if thoracic surgery had not demonstrated its ability to eradicate bronchogenic carcinoma when it has not metastasized The first successful pneumonectomy for lung cancer was reported in 1933 and surgical progress since then has been most gratifying The operative mortality has gradually declined throughout the years until at present it is almost a negligible factor in surgical considerations. Refinements in technique based on a better understanding of pulmonary

function have considerably reduced the hazards of post-operative complications

The fact that the operative mortality for pneumonectomy has been brought within the same range as that of the more common surgical procedures is convincing evidence of the practicability of lung resection The results are even more astounding in consideration of the age group that is usually involved Despite the technical success that has been achieved in pneumonectomy, however, the ultimate survival rates are still low. Many factors may be responsible for this, but the chief one is undoubtedly the presence of metastatic foci, recognized or latent, at the time of surgical intervention It is pointless to evaluate surgical therapy when the lesion has extended beyond the confines of the lung The treatment in these cases is only palliative It may be justified in the hope of making the patient more comfortable and prolonging life, but it is not definitive therapy in the same sense as resection for bronchiectasis or abscess.

Cancer Education

It was hoped that as a result of the intensified efforts in recent years to make the public more symptom-conscious a greater number of patients with early lesions would be found at cancer clinics. Unfortunately this has not been the general trend Neither the well-directed publicity nor the availability of diagnostic services at the large medical centers has succeeded significantly in increasing the number of patients suitable for definitive surgery.

In England, the Joint Consultation Clinic for Neoplastic Diseases of the Brompton and Royal Cancer Hospitals found only 20 resectable cases in the period 1944-9 It was felt, on the basis of this experience, that the expectation of earlier diagnosis in a greatly increased proportion of patients in the near future was unrealistic. Allison, of Leeds, reported a resectability rate of 7 per cent in 1,050 patients between 1941 and 1948, but found a considerable increase in 1949, when the rate was 16 per cent in 178 patients

Patients in the United States also have not presented themselves early for diagnosis or therapy Bloomer and Lindskog, in reviewing their three consecutive series between 1938 and 1949, found that the average duration of symptoms before hospitalization was the same in the early years as in the later years It has not been established, however, that the duration of symptoms, per se, is a deciding factor in prognosis or resectability. Many patients with symptoms of short duration have been found with the most extensive metastatic involvement on the first examination. Conversely, patients with symptoms of one or more years' duration have been found resectable Moore, and others, found that the resected cases had the longest symptomatic histories.

The publicizing of lung cancer symptoms will undoubtedly result in a greater awareness among the population and send more patients to their physicians and to clinics Whether this will increase the number of cases amenable to therapy will depend on numerous factors Probably the most important is the general acceptance that the diagnosis cannot always be confirmed by methods available and that inconclusive, or negative, roentgen, bronchoscopic, and cytologic examinations do not exclude the disease.

In suspected cases, exploratory thoracotomy should be done without undue delay It is of the greatest significance that in so many of the resectable cases the diagnosis was established only by surgical exploration. The proportion of bronchogenic carcinomas found on exploration of obscure pulmonary conditions is considerable Johnson, Clagett, and Good, reporting on 384 patients with varied pulmonary lesions, found 63 lung cancers diagnosed by methods other than thoracotomy and 60 diagnosed only by thoracotomy More than half of the patients in whom the diagnosis could be established only by thoracotomy turned out to be cases of bronchogenic carcinoma

Resectability has been used as an index of early diagnosis but this consideration has been only relative and in contrast to the cases that were too far advanced clinically even to be explored Cases that show metastatic extension do not properly belong in the category of early cases However, a large proportion of the cases resected had visible metastases at the time of operation Half of the cases resected by Overholt in the period 1932–43 had extrapulmonary extension and in the period 1944–8 more than two-thirds had extrapulmonary metastases The number of cases suitable for definitive surgery was, therefore, considerably less than the number resected For the period 1932–48 there were only 55 cases resected without extrapulmonary extension This represented approximately 10 per cent of the total cases presented for therapy.

Survival Rates

It will be many years before an accurate appraisal of survival rates is available. The localization of the tumor, the histologic appearance, the general condition of the patient, and many other variables will have to b considered separately and conjointly The rates of operability, resectio and survival are all closely related to the problem of early diagnosis A ca that is recognized while the tumor is still localized is resectable and has excellent chance for long survival It is, therefore, the internist and the roe genologist who must constantly be alert for suspicious cases It is they, a not the thoracic surgeon, who in the long run determine the survival ra Surgery has succeeded in reducing the operative mortality to an almost consequential figure but has little control over the ultimate survival of patient Meticulous selection of cases for resection might increase the

vival rate but would also deprive a great many patients of the benefits of surgical therapy.

The situation that confronts us in the management of bronchogenic carcinoma is paradoxical. We have available a form of treatment that is rational, practicable, and with relatively low operative mortality. Despite this the number of patients to whom this treatment is applicable is piteously low. The solution is obvious, and it lies in a re-evaluation of diagnostic criteria so that patients may be submitted for surgery while the tumor is still confined to the lung in which it originated.

It is the aim of this volume to correlate the clinical and pathological experiences of the authors with those of other contributors on this subject so that there may be established a better concept of the early phases of bronchogenic carcinoma. The full benefits of surgical progress will be attained only when we have developed the ability to diagnose the resectable case.

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II

Prevalence

Bronchogenic carcinoma was recognized in the nineteenth century but was considered an uncommon occurrence by most clinicians and pathologists Within the past three decades there has been a marked rise in incidence and at present it is the leading form of fatal cancer among males in the United States Primary lung cancer accounts for 10 per cent of the total cancer deaths and more than 20 per cent of the cancer deaths among males between 45 and 70 years of age. Similar increases have been noted in other countries In England and Wales the crude death rate from lung cancer increased from 8 per million in 1900 to 321 per million in 1952

Historical Considerations. Laennec described cancer of the lung in 1805 in the *Dictionnaire des sciences médicales* and, more fully, in 1819 in his famous treatise, *De L'Auscultation médiate.* During the same era the disease was also recognized in England by Baillie (*Morbid Anatomy,* 1796), Burns (*Dissertation on Inflammation,* 1800), Hey (*Practical Observations in Surgery,* 1803), and Abernathy (*Surgical Observations on Tumors,* 1804). In 1837, Stokes (*Treatise on the Diagnosis and Treatment of Diseases of the Chest*) directed attention to the clinical manifestations, and in 1838 Carswell (*Pathological Anatomy*) emphasized the primary nature of the tumor In the fourth edition of *De L'Auscultation médiate* (1838) there is a footnote by Andral which states that since Laennec's first description '. . . the periodical publications have teemed with cases of this disease.'

During the latter half of the nineteenth century many individual cases of lung cancer were reported in England, France, Germany, and the United States by Fuller, Anderson, Auvard, Beale, Beck, Walshe, Behier, Boix, Harris, Ripley, and others Of greater significance was the publication of series of cases denoting increasing recognition. Among the reports were those of Reinhard (25 cases), Wolf (31 cases), Werner (9 cases), Fuchs (8 cases), and Passler (70 cases) In 1897 West reported a collected series of 155 cases from St Bartholomew's Hospital and the *Transactions of the Pathological Society*

In 1912, Adler, in his monograph *Primary Malignant Growths of the Lungs and Bronchi,* described 374 collected cases of primary lung cancer and 207

additional cases classified as 'sarcoma, doubtful and miscellaneous' With some exceptions, most of the latter group appeared to be cases of primary lung cancer In the earlier literature, the word 'sarcoma' signified little more than a fleshy growth and was used freely without specific histologic definition (In a recent study Noehren and McKee found only 34 acceptable cases in the literature since 1912) Although Adler had stressed the frequency of lung cancer as early as 1896, the publication of such a large series of cases created intense interest, which was almost immediately reflected in the publication of additional cases both here and abroad

Rigid diagnostic criteria for the pathological recognition of bronchogenic carcinoma were established by Weller in 1913, and shortly thereafter many diagnoses of tuberculosis, unresolved pneumonia, and pulmonary suppuration were changed to lung cancer after necropsy examination The development of clinical knowledge was an outgrowth of the pathological studies Packard in 1917 described the clinical manifestations in terms of physical signs, roentgen shadows, and bronchoscopic findings In the early 1920's excellent clinical reviews were published by Fishberg and Steinbach, Barron, Childs, Christie, Eloesser, Moise, McCrae, and many others Although bronchoscopic biopsy had been employed before 1910, its importance was not fully realized until Chevalier Jackson popularized the procedure a decade later. Surgical resection for lung cancer had been attempted since the first decade of this century (Brauer, Ders, Friedrich, Sauerbruch, Garré, Meyer) but the first successful pneumonectomy was performed by Graham in 1933

Necropsy Studies

For more than a century, the necropsy examination was the chief source of knowledge of lung cancer Clinical diagnoses were uncommon until relatively recently Of 178 cases collected by Sehrt in 1904, only 6 had been detected during life Ferenczy and Matolcsy found but 18 cases diagnosed clinically out of 80 between 1907 and 1916 and 44 cases out of 150 between 1917 and 1925 Since then, the number diagnosed only at necropsy is still embarrassingly large Farber in 1954 found that of 1,070 cases collected from 19 California hospitals the diagnosis was not made prior to autopsy in over 600 (61 per cent)

Early Statistics The difficulties of differentiating bronchogenic carcinoma from other pulmonary disorders in the nineteenth century probably account for the infrequency of occurrence in the early studies Out of 20,116 autopsies reported from Dresden between the years 1852 and 1894 there were but 45 cases In Munich, during approximately the same period, there were 12,307 autopsies with 8 cases A report from Vienna for the years 1887–1906 revealed 68 cases out of 40,000 autopsies At the University of Minnesota there were no cases of lung cancer in 1,032 autopsies from 1899 to 1911

At the University of Leipzig, the occurrence of lung cancer in all autopsies

was 0 67 per cent from 1900 to 1906. During the period 1919–22, the frequency rose to 1 54 per cent. The proportion of lung cancers to all carcinomas also increased from 5 01 per cent to 9.17 per cent. There were no cases of bronchogenic carcinoma in 606 autopsies at the Johns Hopkins Hospital from 1890 to 1895 From 1910 to 1915, there were 4 cases out of 868 autopsies, and from 1925 to 1930 there were 13 cases out of 2,830 autopsies In the 40-year period studied, the proportion of lung cancer to all carcinomas had risen from 0 to 7 per cent. Similar results were obtained in the autopsy studies in Prague for the period 1894–1943

Recent Statistics The necropsy increase in bronchogenic carcinoma has been very marked since 1930. At the Charity Hospital in New Orleans there were 3 cases (0.047 per cent) among 635 autopsies in 1931, and 17 cases (2 0 per cent) in 825 autopsies in 1938 During this period there was no corresponding increase in carcinoma of the stomach. Olsen reported on autopsy statistics at the Boston City Hospital and found 2 cases (0 21 per cent) from 1900 to 1904, 7 cases (0.73 per cent) from 1920 to 1924, and 38 cases (1.44 per cent) from 1930 to 1934. The frequency of primary lung cancer to all carcinomas had increased from 3 5 to 12.96 per cent. At the Veterans' Bureau, Matz found the frequency of lung cancer to be 6 4 per cent of all carcinomas during the years 1927–31 and 15.8 per cent for the years 1932–7. In the last year of the study, the frequency had risen to 23 4 per cent.

The statistical data is in general agreement that there has been a notable increase in the occurrence of bronchogenic carcinoma as observed at necropsy In some institutions the rise was gradual whereas in others there were sharp peaks, particularly since 1930 For example, in a collected series of 517 cases reported by Menne and Anderson there were only 3 instances of bronchogenic carcinoma in the period 1920–25 and 407 cases in the years 1936–40 Notable increases have also been reported by Pekelis, Loizaga, and Hruby and Sweany.

There is still considerable variation in the frequency of bronchogenic carcinoma as reported by different observers, with the rates ranging from 3 per cent to 42 25 per cent of all carcinomas. In most general hospitals, however, the figure is approximately 10 per cent. At the New York City Hospital for the period 1920–48 the frequency was 11 per cent of all carcinomas and 1 6 per cent of all autopsies Koletsky, at the Cleveland City Hospital, found the frequency to be 9 4 per cent of all carcinomas and 1.3 per cent of all autopsies. At the Cook County Hospital the frequency was 11 47 per cent of all carcinomas It is of interest that of 1,826 autopsies at the New York Cancer Institute between 1932 and 1949 there were only 94 cases (5 per cent) In the last five years of the study the incidence was 11.5 per cent.

A report by Steiner from the Los Angeles County Hospital covers the period 1918–46 There were 36,864 necropsies which included 6,023 malig-

nancies, of which 508 (8 4 per cent) were cancers of the lung Between the years 1918 and 1922, there were no cases of lung cancer, although cancer was found in 11 2 per cent of the autopsies During the period 1923–7, cancers of the lung comprised 4 3 per cent of the total malignancies and 0 6 per cent of total autopsies The succeeding years showed progressive increase of lung cancer, and between 1943 and 1946 it had risen to 11.3 per cent of the total malignancies and 2 3 per cent of the total necropsies. No comparable increases were found for carcinoma of the stomach, bowel, pancreas, or for brain tumors.

Interpretation of Data

The above-mentioned and similar statistics have been cited as proof that the incidence of bronchogenic carcinoma is increasing This conclusion is erroneous if based solely on autopsy studies. These figures show only that there has been a marked increase in the frequency of necropsied cases of lung cancer They do not prove that there has been an increase of the disease in the general population Macklin has shown that autopsy statistics, because of their selective character, may be subject to gross misinterpretation In the case of bronchogenic carcinoma many factors present themselves as explanations of how an increase in autopsy incidence may occur without implication of the general population

1 Bronchogenic carcinoma was not generally recognized until the end of the nineteenth century
2. The increasing interest in the disease because of new diagnostic and therapeutic measures resulted in the hospitalization of more patients
3 The introduction of antibiotic drugs resulted in fewer deaths from infectious disease and proportionately more deaths from cancer
4 The successful treatment of infectious disease at home made more hospital beds available for cancer patients
5 The interest of the clinician in obtaining an autopsy in a suspected case of bronchogenic carcinoma was greater than that in a more obvious cancer
6 The increasing age of the population resulted in the hospitalization of more elderly patients than previously
7 The selective policy of hospitals for interesting cases resulted in greater admission of lung cancer
8 Autopsy statistics are based on hospital populations, which form only a small segment of the total population.

In some studies, the necropsy frequency of lung cancer was as high three decades ago (Table 1) as is found at present Jaffe found in Vienna a frequency of 10 73 per cent of all carcinomas between the years 1915 and 1918 Fifteen years later he reported from Chicago a frequency of 11 47 per cent

TABLE I *Lung Cancer Necropsy Statistics before 1925*

YEAR	AUTHOR	PLACE	PER CENT OF ALL CARCINOMAS
1897–1906	Biberfeld	Berlin	2.1
1907–1916	Biberfeld	Berlin	6.0
1898–1902	Junghanns	Dresden	11.62
1912–1917	Junghanns	Dresden	13.58
1918–1922	Junghanns	Dresden	16.58
1900–1911	Kikuth	Hamburg	3.8
1912–1923	Kikuth	Hamburg	5.8
1906–1910	Probst	Zurich	0.13
1911–1915	Probst	Zurich	3.34
1916–1920	Probst	Zurich	6.12
1900–1906	Seyfarth	Leipzig	5.10
1914–1918	Seyfarth	Leipzig	11.23
1909–1914	Sonnenfeld	Berlin	4.68
1920–1924	Sonnenfeld	Berlin	8.08
1903	Hanf	Berlin	3.7
1919	Hanf	Berlin	5.5
1923	Hanf	Berlin	9.0
1895–1904	Holzer	Prague	1.04
1905–1914	Holzer	Prague	2.36
1915–1924	Holzer	Prague	6.69
1900–1904	Olson	Boston	3.50
1920–1924	Olson	Boston	7.07

between the years 1929 and 1934 Bonser, in Leeds, found a 7 per cent frequency between 1893 and 1902, and Maxwell and Nicholson reported a 10 per cent frequency at the St Bartholomew's Hospital before World War I.

Passey and Holmes emphasized the selective character of necropsy statistics and attempted to avoid the more obvious pitfalls by concentrating on hospitals that had a consistently high percentage of post-mortem examinations before interest in lung cancer had become intensified. In this manner they hoped to obtain an accurate reflection, through several decades, of the relation between the necropsy frequency of bronchogenic carcinoma and the total hospital admissions.

The results of the survey showed no striking changes in the percentage frequency of lung cancer through the period 1894–1928. The total number of lung cancers was increased but only in proportion to the total hospital admissions. In the period 1894–8, the total admissions numbered 315,059 and the total lung cancers at necropsy numbered 173 (.055 per cent), whereas in the period 1924–8 the total hospital admissions were 786,912 and there were 552 lung cancers found at necropsy (.07 per cent). It is significant that no real increase in percentage occurred until the last period of the survey, which coincided with the abrupt rise in interest in the disease clinically and pathologically.

Steiner reviewed 5,515 autopsies at the University of Chicago and found 126 cases (2.3 per cent) of primary lung cancer. The incidence among all carcinomas was 10.3 per cent. The study covered forty years and was divided into consecutive periods of five years each. Although a marked increase in

the number of cases occurred in the last fifteen years of the survey (1927–41), the frequency of lung cancer in terms of percentage of all tumors showed only a slight increase in males After consideration of all factors such as total necropsies, sex, age, and total malignancies, Steiner concluded that there had been no real increase in the forty-year period.

Clinical Studies

Bronchogenic carcinoma entered the realm of clinical medicine in the first quarter of this century There were many reports of cases in the literature before that time, but as far as the general practitioner was concerned the disease was a rare curiosity Interest in pulmonary carcinoma became manifest as greater opportunities for diagnostic confirmation were made available by bronchoscopy, roentgenology, and pathology In the succeeding years thousands of cases were diagnosed and a vast literature began to accumulate

Mortality Rates Since the death registration area was established in the United States approximately fifty years ago, the recorded mortality from cancer has more than doubled from 64 per 100,000 in 1900 to 145 per 100,000 in 1953 This rise was in a large measure a reflection of the increase in the proportion of elderly persons in the population In the first part of the twentieth century, the increase in the cancer mortality rate was evident in both sexes, but the rate of increase among white females began to diminish, and since 1930 the mortality rate for white females has decreased 4 per cent after correcting for changes in the age composition of the population (Dorn)

Among white males, the trend in the cancer mortality rate is still increasing except for specific instances In cancer of the skin, buccal cavity, and pharynx there has been a definite decline in the age-adjusted mortality rate in both males and females Although the mortality rate from malignancy of the gastro-intestinal tract increased for males during the first quarter of the century since then, the age-adjusted rate has been fairly constant

The most dramatic increase in cancer mortality rate occurred in cancer of the lung When the death registration area was first established in 1900, the reporting of a case of lung cancer was almost a rare occurrence Even in 1914, there were only 371 lung cancers when the total number of malignancies was 52,420 and the registration area comprised 67 per cent of the population of the United States (Gover) Since then lung cancers have been reported with increasing frequency and in 1953 represented approximately 10 per cent of the total cancer deaths

The increase in lung cancer deaths has occurred predominantly among males In both the white and the non-white population, the mortality rate for males is 4 4 times the rate for females This difference between male

and female mortality rates has more than doubled in the past quarter of a century.

All clinical studies agree that cancer of the lung is primarily a disease of late adult life (See Chapter III for compilation of cases occurring in early decades) Below the fifth decade of life, lung cancer does not figure as a significant cause of death among white males. After age 40, the death rate rises dramatically, reaching a maximum in the eighth decade (Table 2). Although the rate declines after the eighth decade for white males, it continues to increase for white females for the remainder of the life span However, if the statistical data is computed by tracing a white male cohort throughout its lifetime, the death rate continues to increase even after the eighth decade.

The recorded mortality rates from lung cancer are almost 30 per cent higher for whites than non-whites but this is also found in all forms of cancer This difference is decreasing, however, as a result of greater availability of diagnostic facilities and increase of the life span of the non-white population

From 1930–32 to 1939–41, the age-adjusted mortality rate for lung cancer among white males increased 168 per cent, or about 18 per cent annually. The corresponding increase for white females was 67 per cent, or about [illegible] per cent annually Although these increases were large, they were smaller than had occurred in the two previous decades Between 1914 and 1930–32 the age-adjusted mortality rate for white males had increased 393 per cent, or about 23 per cent annually The corresponding increase for white females was 228 per cent, or about 13 per cent annually In general, the increases were confined to males over 35 years and females over 45 years. At the younger ages, the death rates from lung cancer were lower in 1939–40 than they had been in 1930–31 In 1939–40, the lung cancer death rate for white males over 50 years was 25 per 100,000, whereas the rate for all cancers was 119 per 100,000 Among white females over 50 years, the lung cancer death rate was 11 per 100,000 and 129 per 100,000 for all cancers

Between 1940 and 1949, the rate of increase in mortality from lung cancer declined and was only about one-half that of the previous decade, indicating a termination of the period of rapid rise. Among white males, the death rate at ages under 35 was no higher in 1949–51 than it had been two decades previously There was no recorded increase among white females from 1939 to 1949, except among those over 35 years of age In the non-white population, the rise in death rate from lung cancer was confined to persons over 30 years. The statistical studies by Dorn definitely indicate that the increase in mortality from lung cancer is slowing down and is occurring only in the older age groups.

Morbidity Rates. According to morbidity studies by the National Cancer Institute the incidence of lung cancer is five times as great in the male as in

TABLE 2 *Number of Deaths per 100,000 Population from Cancer of the Respiratory System by Age, Sex, and Color, United States, 1949–51 (Dorn)*

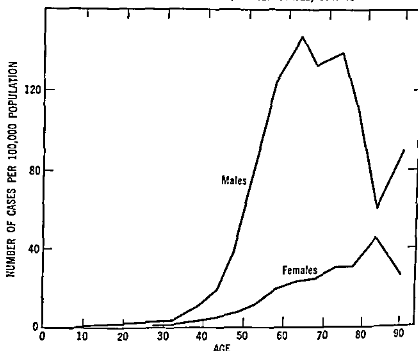
	TOTAL RESPIRATORY					LUNG					LARYNX				
	TOTAL	WHITE		NON-WHITE		TOTAL	WHITE		NON-WHITE		TOTAL	WHITE		NON-WHITE	
		MALE	FEMALE	MALE	FEMALE		MALE	FEMALE	MALE	FEMALE		MALE	FEMALE	MALE	FEMALE
0–4	0.1	0.1	0.1	0	0	0.04	0.03	0.1	0	0	0.002	0.003	0	0	0
5–9	0.1	0.1	0.05	0.04	0.1	0.04	0.06	0.03	0	0.01	0.002	0.01	0	0	0
10–14	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.2	0	0.003	0	0.01	0	0
15–19	0.2	0.3	0.2	0.4	0.1	0.1	0.1	0.1	0.3	0	0.006	0	0.01	0	0
20–24	0.3	0.4	0.3	0.6	0.2	0.2	0.3	0.2	0.5	0.1	0.02	0.01	0.01	0.1	0.03
25–29	0.5	0.6	0.3	1.2	0.5	0.4	0.5	0.3	0.8	0.3	0.02	0.02	0.01	0.1	0
30–34	1.2	1.6	0.7	1.0	1.0	1.0	1.4	0.7	1.6	0.8	0.03	0.01	0.04	0.1	0.1
35–39	3.0	4.4	1.4	6.1	1.8	2.6	4.0	1.5	5.2	1.4	0.1	0.2	0.05	0.4	0.1
40–44	7.3	11.3	3.0	12.3	4.8	6.4	10.0	3.2	10.5	4.2	0.5	0.7	0.2	1.2	0.1
45–49	18.0	27.0	5.1	25.7	6.4	14.4	24.3	5.1	22.3	5.5	1.0	1.8	0.2	2.0	0.4
50–54	30.3	51.7	8.3	55.5	11.7	27.0	46.4	8.1	49.1	10.0	2.3	4.0	0.4	5.5	0.9
55–59	47.0	82.1	12.4	72.5	14.5	41.9	73.5	11.6	65.7	12.0	3.5	6.4	0.6	5.4	1.6
60–64	62.9	110.4	17.7	70.1	14.7	55.5	97.5	16.4	68.9	12.0	5.3	10.0	0.7	6.9	1.1
65–69	67.4	117.4	22.7	84.1	18.5	59.8	102.1	19.6	71.3	16.0	6.3	12.2	0.9	8.5	1.4
70–74	72.4	122.9	30.8	64.7	19.7	60.6	101.0	25.5	49.3	16.2	8.1	16.0	1.2	10.8	1.7
75–79	71.1	111.7	39.6	63.1	19.0	59.2	89.0	29.1	51.3	17.5	8.6	16.8	2.0	7.7	0.5
80–84	62.1	96.0	40.3	92.4	10.7	49.3	71.2	24.1	27.0	12.5	8.5	17.1	2.3	4.5	3.3
85 and over	61.7	93.5	43.8	29.1	21.0	41.3	67.1	29.4	21.1	17.3	9.2	19.5	3.0	3.5	1.2
All Ages															
Crude	13.9	23.7	3.5	14.4	3.4	12.0	20.6	4.6	12.3	2.8	1.2	2.3	0.2	1.4	0.7
Adjusted	13.9	23.5	5.0	18.4	4.4	12.0	20.3	4.3	15.6	3.7	1.2	2.3	0.2	1.8	0.3

Age-adjusted rates are based on total population of continental United States, 1 July 1949

the female population after adjusting for differences in the age distribution of the two sexes Among males the morbidity rate increases rapidly from the fourth decade to the seventh and eighth decades and then declines (Chart 1). The morbidity rate for females increases until the ninth decade. The largest differential in incidence rate was found in the first half of the seventh decade, with a ratio of 7.1 in favor of males Between 1937 and

Chart I

MORBIDITY RATES (incidence) FOR CANCER OF THE LUNG AND BRONCHUS, UNITED STATES, 1947 48



1947 the morbidity rate of lung cancer among males increased 100 per cent and among females 55 per cent

Morbidity data for cancer are not available for the total population of the United States Studies conducted by the National Cancer Institute in 1947 and 1948 in 10 metropolitan areas with an aggregate population of approximately 15 million persons yielded an annual incidence rate of newly diagnosed cases of 29 per 100,000 for males and 6 5 for females. On the basis of these figures, it was estimated that 30,000 new cases of lung cancer were diagnosed in the United States in 1953

Ratio of Lung Cancer to Total Cancers In 1930 the total number of deaths in the United States from cancer was 114,186 The total number of lung cancer deaths was 2,837 (2 5 per cent), of which 1,753 occurred in white

males and 982 in white females The occurrence among non-whites was almost negligible, totaling 102 deaths among both sexes

Within a period of five years, the over-all picture had changed considerably. By 1935, the total number of cancers had increased from 114,186 to 137,649 cases (20 per cent), and cancer of the lung had increased from 2,837 to 5,049 cases (78 per cent) The lung cancer gains occurred in all groups and were numerically greatest in white males, from 1,753 to 3,331 cases The greatest proportionate increase, however, was among the non-white males The increase in lung cancer in non-white females was negligible in 1935, as was the total number (53 cases)

In the succeeding years the increase in deaths from cancer of the lung was far greater than the increase from all forms of cancer It was also evident that the increase was following a pattern in regard to sex and race distribution (Table 3). In 1940, the total cancer deaths were 158,335, an increase

TABLE 3

Number of Deaths from Lung Cancer (United States)

YEAR	WHITE		NON-WHITE		TOTAL
	MALE	FEMALE	MALE	FEMALE	
1930	1,753	982	65	37	2,837
1935	3,331	1,505	160	53	5,049
1940	5,767	1,902	290	97	8,056
1945	8,692	2,736	514	188	12,130
1950	13,981	3,162	941	229	18,313

Increase of deaths between 1930 and 1950 = 500 per cent

Number of Deaths from All Cancer (United States)

YEAR	WHITE		NON-WHITE		TOTAL
	MALE	FEMALE	MALE	FEMALE	
1930	48,962	58,528	2,326	4,370	114,186
1935	59,798	69,331	3,140	5,380	137,649
1940	71,109	76,674	4,297	6,255	158,335
1945	80,432	84,602	5,394	7,036	177,464
1950	98,799	94,898	8,172	8,864	210,733

Increase of deaths between 1930 and 1950 = 85 per cent

of 15 per cent since 1935 The deaths from cancer of the lung numbered 8,056, an increase of 60 per cent since 1935 This latter increase occurred

chiefly among the white males. There was an increase of 427 cases among the white females, an increase of 130 among the non-white males; and an increase of 44 cases among the non-white females.

In 1945 the number of total cancer deaths was 177,464, an increase of 12 per cent since 1940 The deaths from cancer of the lung numbered 12,130, an increase of 50 per cent since 1940. Again the increase was chiefly among the white males (2,925 cases) The increase among white females was moderate (804 cases) and among the non-whites it was slight. Among the non-white males the total death registration in 1945 for cancer of the lung was 514, an increase of 224 cases since 1940 For the non-white females, the number was 188, an increase of 91 cases since 1940.

A clear picture of the trend is obtained by reviewing the changes between 1930 and 1950. In 1930 the total deaths from all cancers was 114,186, and in 1950 it was 210,733, an increase of about 85 per cent. The deaths from lung cancer in 1930 numbered 2,837, and in 1950 the number was 18,313, an increase of about 500 per cent. In 1930 cancer of the lung represented 3 5 per cent of all cancers in white males and 1 6 per cent in white females In 1950 the percentage for white males was 14 3 and for white females it was 3 3 Corresponding increases were noted in the non-white population

Accuracy of Statistics Vital statistics concerning lung cancer obtained in the early decades of this century must be carefully evaluated in view of (1) the general inability to diagnose the disease and (2) the absence of a specific statistical category in which to record it. The more recent statistical data may also be misleading, for in spite of the great diagnostic achievements of the past twenty-five years a great many cases remain undiagnosed The detection of lung cancer in nonhospitalized cases presents great problems, and errors are frequently made both in diagnosing malignancy and in failing to recognize it. The widening experience with exploratory thoracotomy has repeatedly demonstrated the difficulties of accurate diagnosis in pulmonary disease However, the improvement in diagnostic techniques and the wide dissemination of this knowledge are gradually narrowing the gap between the statistical data and the actual incidence of this disease

Distribution of Lung Cancer

Sex. Bronchogenic carcinoma is predominantly a disease of males There has been a unanimity of reports bearing out this observation, and Ochsner and DeBakey, in a collected series of 8,575 cases, found 6,769 males (78 9 per cent) and 1,806 females (21 1 per cent) The ratio of 4.1 was also reported by Simons, Steiner, Tripoli and Holland, Dick, Fried, and others In the series of 210 cases observed at the City Hospital and at the New York City Cancer Institute there were 184 males and 26 females, which gave a ratio of 7:1. Several authors have reported ratios of 10:1 and higher.

The prevalence of bronchogenic carcinoma in the male has been the

subject of much speculation The explanation that it is due to a greater smoking habit among males is highly improbable It has also been suggested that the greater susceptibility of the males is due to a sex-linked character. Necropsy reports have shown differences in pathological behavior of the disease among males and females. According to Fried the reason for male preponderance lies in the fact that bronchogenic carcinoma is a disease of late adult life. The incidence of cancer is high in females, but it usually occurs at an earlier age with mammary or genital involvement Many females who are susceptible to cancer are thereby eliminated from acquiring lung cancer, because they do not reach the age group in which the condition is commonly found

Age Bronchogenic carcinoma occurs most often in the fifth, sixth and seventh decades of life but has been found in every age group including infancy Simons, in a collected series of over 5,000 cases, found that 80 per cent occurred between the ages of 40 and 70 Brunn reported a series of 576 cases, with 62 per cent between 40 and 60 years of age Olson found 73 8 per cent in the fifth, sixth, and seventh decades, and similar findings were reported by Weller, Breckwoldt, and Fischer. Cancer of the lung occurs under the age of 40 but is not common It is rarely found in the first three decades of life

Out of 4,307 cases collected by Ochsner and DeBakey there were only 163 instances under the age of 30 While four-fifths of the patients were between the ages of 40 and 70, the authors also point out that approximately 40 per cent were under 50 years of age Singer found 13 patients under 30 years in a collected series of 361 cases Bronchogenic carcinoma in children has also been reported by Beardsley, Lereboullet, Cathala and Ducas, and others In the 210 cases studied at the New York City Hospital and the New York Cancer Institute there were no patients under 30 years Eighty per cent of the cases were over 50 years of age

Race Bronchogenic carcinoma has been found in all races but is most common in the white race In the United States, practically all reports show a preponderance of white patients At the Cook County Hospital it was found that 9 per cent of 135 patients with lung cancer were colored, whereas the Negro hospital population was 30 per cent Halpert reported 3 170 necropsies among whites, with 53 cases, and 4 263 necropsies among Negroes, with 39 cases At the Harlem Hospital in New York City, where the Negro population is almost 90 per cent, the necropsy frequency of bronchogenic carcinoma was practically equal between the Negroes and the whites The National Office of Vital Statistics reported for 1950 a total of 17,143 deaths from lung cancer among whites and a total of 1,170 deaths among non-whites In our study of 210 cases there were 197 whites, 12 Negroes, and 1 Chinese The ratio of whites to non-whites was 15 1

Although some of the statistical evidence points to a natural immunity of the Negro, no conclusions are justified until the life span of the two

races is approximately equal. Bronchogenic carcinoma is most prevalent in the later decades of life and in general the Negro population does not live so long as the white population Tuberculosis and other infectious diseases are responsible for higher death rates among Negroes and prevent them from reaching the cancer age. The effect of the difference in age distribution can be eliminated by the use of age-specific morbidity or mortality rates.

The clinical impressions on racial susceptibility are gradually being revised as more data are accumulated on the non-white population Greater recognition of the disease and consideration of the age survival factor will probably demonstrate in the future a more equal distribution of the disease among all races.

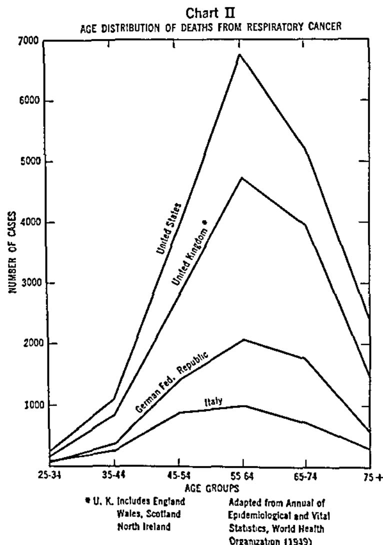
Geographic The prevalence of lung cancer throughout the world has, in general, shown a progressive increase similar to that observed in the United States. This increase has occurred in areas with wide variations in habits, occupations, and climate. It has occurred in countries where cigarette consumption has gone up tremendously (United States, Canada, Italy) and it has occurred in countries in which cigarette consumption has been fairly stationary (Germany, Austria, Turkey, Japan). The increase is undoubtedly due to the same factors that prevail everywhere, namely, improved methods of diagnosis and increase in the life span of the population

From 1938 to 1949, the deaths from lung cancer increased approximately 200 per cent in Canada, Denmark, and Finland and 100 per cent in Austria, Italy, Norway, and Ireland In the United Kingdom, including England, Wales, Scotland, and Northern Ireland, the increase was over 100 per cent during this same period. It was also over 100 per cent in the Netherlands, New Zealand, and the European population of the Union of South Africa

In some areas of the globe the disease is still considered a rarity. In a study of 422 histologically proved cancers in Bangkok, Thailand, Velhos found only one lung cancer A necropsy report from Hong Kong showed but 2 lung cancers out of 1,133 malignancies. A later study at the Peiping Union Medical College revealed 16 cases between 1936 and 1940 with 8 of the cases diagnosed during the year 1939–40. Many more cases were suspected clinically but lacked histological confirmation. Out of 11,599 autopsies in a study in the Philippine Islands between the years 1907 and 1925 there was found but one case of lung cancer Sison and Monserrat found 2 cases in 1927.

The relation between the incidence of new cases and improved diagnostic facilities was demonstrated by Ibrahim in a report from the Dacca Medical College Hospital in East Pakistan. During an 18 months' study involving 362 pulmonary cases there were found 20 cases of bronchogenic carcinoma. The sex, age, and occupational distribution corresponded to reports elsewhere, namely predominance of males, occurrence in late adult

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carcinogens from tarred roads and automobiles were conspicuously absent Out of the 20 cases there were 14 who did not smoke, 4 occasional smokers and only 2 heavy smokers Cigarette smoking in East Pakistan is rare, the popular method utilizes the *hukka*, a pipe in which the smoke is filtered through water before inhalation

races is approximately equal Bronchogenic carcinoma is most prevalent in the later decades of life and in general the Negro population does not live so long as the white population Tuberculosis and other infectious diseases are responsible for higher death rates among Negroes and prevent them from reaching the cancer age The effect of the difference in age distribution can be eliminated by the use of age-specific morbidity or mortality rates

The clinical impressions on racial susceptibility are gradually being revised as more data are accumulated on the non-white population. Greater recognition of the disease and consideration of the age survival factor will probably demonstrate in the future a more equal distribution of the disease among all races

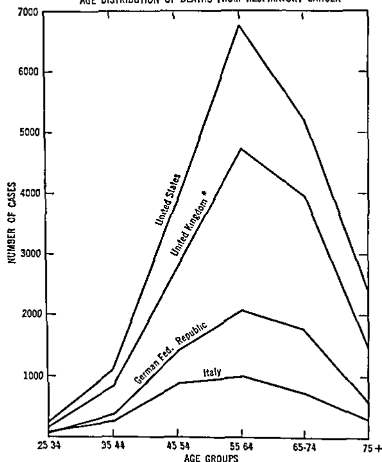
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Of considerable *interest is the comparison of the age distribution of the* lung cancer cases in various countries (see Chart 2). In practically every country the greatest number of cases is found in the sixth and seventh decades with the peak distribution *between 55 and 65 years Statistics* gathered by the World Health Organization shows a similar curve of distribution in countries as far apart as the United States, Finland, Japan, and Australia These figures make it apparent that the incidence of lung cancer is directly related to the percentage of the population in the older age groups.

INCREASED INCIDENCE OF LUNG CANCER

Bronchogenic carcinoma was unrecognized clinically until the early twentieth century Since 1925 there has been a dramatic upswing in the incidence *of the disease It is unrealistic to compare incidence statistics of the* present with those of three decades ago, when the means to diagnose the disease were not available Diagnostic roentgenology, bronchoscopy, tissue biopsy, cytological studies, and thoracotomy are investigative measures of recent vintage Smithers stated that at the Brompton Hospital there were 29 bronchoscopies between 1926 and 1929 while at present more than 800 are done each year King and Newsholme pointed out in 1893 that when a cancer becomes diagnostically accessible its incidence automatically increases

General pathological recognition of the disease before 1925 was also scant, but many institutions showed a high frequency before World War I (Wolf, Passey and Holmes, Ferenczy and Matolcsy) and a progressive increase during the late nineteenth and early twentieth centuries (Karrenstein, *Berblinger, Kikuth*)

Although much of the increased incidence of lung cancer is relative, i e due to improved diagnostic methods, a considerable part of the increase is real Lung cancer is a disease of later life and the number of potential candidates is steadily increasing In 1900 there were only 3 million people aged 65 or over in the United States while at present there are 13 million. It is estimated that the number will reach 20 million by 1975.

Vital statistics and necropsy studies leave little doubt about the marked increase of cancer of the lung in recent years The question yet to be answered is whether this increase is due primarily to the diagnosis of more cases or to the actual existence of more cases *The factors to be considered* include (1) smoking, (2) inhalent carcinogens, (3) inflammatory metaplasia, (4) progress in diagnosis, (5) longevity, (6) occupational exposure.

Smoking The involvement of smoking in lung cancer dates back almost half a century Cigar and pipe smoking were formerly implicated, but in recent years the emphasis has shifted to cigarettes. The subject has been dramatized in both medical and lay publications and considerable literature has accumulated The evidence is presumptive and is based largely

on the following considerations: (1) the increase in cigarette consumption and in lung cancer in recent decades, (2) the high proportion of smokers among lung cancer patients, and (3) the experimental production of cancer with tobacco tar The prodigious increase in the use of cigarettes has provoked much speculation about its possible relationship to the increase in lung cancer However, there are many factors to be considered before any definitive conclusions can be reached.

The relationship between this increased incidence and the rise in cigarette consumption is purely speculative Both in this country and in England the death rate from lung cancer has increased at a far greater pace than has the consumption of tobacco Analysis of international reports reveals little correlation between the per-capita consumption of cigarettes and the death rate from lung cancer. The incidence of lung cancer appears to be related far more to the diagnostic facilities available The establishment of a medical center in an undeveloped area is often followed by a sudden increase in the incidence of lung cancer It has often been stated that the incidence of cancer is in direct proportion to the number of doctors per 100,000 of population

Numerous clinical studies (Wynder and Graham, Doll and Hill, Mills and Porter, Hoffman, Schrek, Watson, and others) have been presented purporting to demonstrate a causal relationship between lung cancer and smoking The reports, in general, showed that the proportion of smokers, especially heavy smokers, was higher in the cancer patients than in the control groups Although the differences between the two groups were small, the authors considered them to be statistically significant and concluded that the risk of acquiring the disease was directly proportionate to the number of cigarettes smoked

In the report of Doll and Hill there were 1,357 male cancer patients, 1,350 of which were smokers There was an equal number of controls, 1,296 of which were smokers The difference between the two groups was 54 patients Among the females (108 cases in each group) there were 68 smokers among the cancer patients and 49 smokers among the controls—a difference of 19 patients The cancer groups contained more heavy smokers, but the control group also contained a significant proportion of heavy smokers.

Wynder and Graham found that 96 5 per cent of their male cancer patients had smoked more than 10 cigarettes daily for more than 20 years, as compared with 73 7 per cent of the controls They also found that while 51 2 per cent of the cancer patients had smoked 20 cigarettes daily for at least 20 years only 19 1 per cent of the male controls had smoked that much Mills and Porter found 12 per cent more cigarette smokers in their cancer group than in the controls When the statistics were evaluated with respect to age groups, however, the difference disappeared and some of the age groups showed more heavy smokers among the non-cancer patients

In a 20 months' follow-up study of 187,766 white men aged 50 to 69, Hammond and Horn found 167 deaths attributed to lung cancer, of which 57 were verified microscopically. The lung cancer death rate was higher among men with a history of regular cigarette smoking and still higher among men who smoked one pack or more daily at the time of questioning. The authors conclude that regular cigarette smoking produces an increase in death rates from lung cancer, owing to a cause and effect relationship

In a recent study, Mills reported definite correlation between lung cancer and air pollution The death rate was higher for most occupational groups residing in slum areas and highest for the groups with the greatest degree of exposure to pollution Laborers showed a death rate from 2 5 to 3 5 times higher than professional groups in both clean and dirty areas of the city This study illustrates the number of possible factors that may influence statistical studies on lung cancer.

The reports on lung cancer and smoking are concerned with only two variables, whereas a great many are undoubtedly involved. A statistical correlation does not imply a cause and effect relationship The validity of the results in the smoking surveys is also subject to criticism because of (1) manner of selection of controls, (2) method of quantitative estimation of tobacco consumption, (3) impossibility of establishing onset of disease; (4) unintentional bias, (5) diagnostic errors in both control and cancer groups sufficient to affect the small differences; and (6) predominance of male cases in surveys.

One of the arguments put forth in favor of the smoking theory is the prevalence of the disease in males, attributing the sex difference to their heavier smoking habits Although the incidence of smoking among females has steadily increased since World War I, the ratio of lung cancer between the sexes is still predominantly in favor of the males This has occurred despite the increased incidence of the disease in women. If smoking were of etiological significance there should have resulted some decrease in the sex ratio over a period of years. However, recent statistical studies show the ratio to have actually increased. The data concerning smoking and lung cancer show the percentage of smokers with lung cancer and not the proportion of smokers who develop lung cancer.

Carcinogenic agents can be formed from organic materials by subjecting them to a process of destructive distillation and combustion In the act of smoking, tobacco is subjected to a similar reaction and many attempts have been made to demonstrate a carcinogenic substance in tobacco tar

Helwig painted pipe tar and tobacco distillate on rabbits and mice for periods ranging from four months to a year and obtained either proliferative changes or benign ulcers Cooper produced one epithelioma out of 50 mice painted with tobacco tar 66 times Bogen and Loomis were also unsuccessful in producing malignant changes in mice and rabbits with tobacco tar Sugiura subjected 168 mice to repeated painting for 90–500

days and obtained one squamous carcinoma at the site of application Flory obtained many papillomas or 'carcinomatoid' growths in rabbits but no carcinomas. He found two squamous cell carcinomas in mice but his work, in general, confirmed the previous studies in regard to the low carcinogenic effect of tobacco

The most successful induction of skin cancer in mice thus far was produced by Wynder and Graham, who painted the backs of mice with 40 mg of tobacco tar condensate three times a week At the end of two years, 44 per cent of the mice had developed skin cancer The results show that in the dosage and technique utilized tobacco tar is carcinogenic for a particular strain of mice The relation of this experiment to bronchogenic carcinoma remains to be established

Campbell exposed mice to fumes and tarry matter from cigarette smoke 7 hours a day for 5 days a week At the end of the experiment (829 days), 17 of the exposed animals and 11 of the controls had lung cancer. In both groups, lung cancer developed only in the older animals, i e after the second year of life There were no cancers in the younger mice and Campbell attributed the occurrence of lung cancer in the mice more to old age than to tobacco Pathologically, lung cancer in mice resembles only remotely bronchogenic carcinoma in the human

Inhalent Carcinogens The inhalation of irritant gases, particularly those from automobile exhaust pipes and factory combustion motors, has also been claimed as a cause for the increased incidence The exposure to these gases is so universal, however, as to raise greater doubts of the etiological importance In the city of Pittsburgh, which is notorious for its dust and smoke, the incidence of bronchogenic carcinoma was found far lower than in many other large cities Tarring of roads has also been included in the etiological list because of the definite carcinogenic effect of tar in experimental studies This has been refuted by Passey and Holmes, who reported that in Great Britain the increased incidence of lung cancer preceded tarring of the roads, by Konrad and Franke, who observed an increased incidence without a corresponding increase of tarring or of automobiles, and by Davidoff and Uspensky, who found an increasing incidence of pulmonary cancer in areas without tarring of the roads and without automobiles

Inflammatory Metaplasia Broncho-pulmonary inflammatory disease may produce metaplasia of the bronchial epithelium and cellular structure, which simulates carcinoma This was observed in patients who died of influenza, and it gave rise to a consideration of the possible relationship between the influenza epidemic of 1918–19 and the subsequent increase in bronchogenic carcinoma However, later studies have shown the occurrence of influenza in patients with lung cancer to be relatively insignificant

Tuberculosis and fungus infections have also been implicated in various case reports The not uncommon co-existence of tuberculosis and lung can-

cer led to much speculation regarding causal relationship, but this has largely been discarded

Progress in Diagnosis The epidemic-like increase in incidence as shown by the preceding studies paralleled the increase in knowledge of the disease Bronchogenic carcinoma was a rarity to most pathologists in the early part of this century Once the origin of the tumor was recognized the reports began to multiply Pathological knowledge of malignant disease was increasing at this time, and in many institutions the sudden increase in the necropsy incidence of lung cancer occurred simultaneously with the establishment of a pathology department There was an even greater lag in recognition of the disease in clinical medicine The dissociation of carcinoma from other chronic pulmonary diseases took place within the past three decades It was during this period that diagnostic techniques were improved and each year utilized with greater frequency, and it was during this period that the incidence increased so greatly.

Longevity The increase in lung cancer has occurred chiefly in the older age groups The average life span of the population in the United States has increased steadily and is now well past 65 years The frequency of lung cancer has increased because there have been more potential candidates, i e. more susceptible people reaching the cancer age In the younger age groups, there has been no increase As the average length of life increases we must anticipate a greater number of cases of bronchogenic carcinoma as well as other malignancies The incidence of lung cancer apparently increased to a greater extent than other cancers because of its more recent recognition After a period of years its rate of increase will undoubtedly become smaller

Occupational Exposure The 210 cases of bronchogenic carcinoma in our series were classified according to occupation with the vain hope of obtaining some etiological clue In 93 instances, the patients were either unemployed or the occupation was not listed Among the 117 employed, there were 50 different occupations ranging from business executive to grave digger. Eighteen of the 26 female patients were housewives Most of the patients had been engaged in some type of manual work such as laborer, porter, or mechanic, which paralleled the occupations of the general hospital population In England, Brockbank found in an occupational classification of 898 cases of primary lung cancer that the majority of patients were laborers or manual workers of some sort. The professional and white-collar classes were in the minority This, again, may be a reflection of the occupations of the hospital population rather than of etiologic significance.

Workers in the Schneeberg and Joachimsthal mines have for centuries been very susceptible to chronic pulmonary disease, with high mortality rates. Official studies showed the necropsy frequently of carcinoma to be as large as 60 per cent in some years The problem of lung cancer in the Schneeberg and Joachimstal mines has been the subject of much investi-

gation but no definite conclusions have been reached Lorenz made an exhaustive study and was unable to arrive at a decision concerning the effects of the chronic radon exposure in the mines. The role of heredity must be considered in the evaluation of the high incidence of the disease, in view of the inbreeding that has taken place for centuries in the mining localities

Exposure to silica and asbestos dust has also been implicated as an etiological factor on the basis of case reports of co-existence of pneumonoconiosis and carcinoma The number of cases reported is too small, however, to warrant causal relationship. Furthermore, the comprehensive studies on occupational dust by Vorwald and Karr revealed no evidence of an etiological association between the two conditions More recently chromium has been suggested as an etiological agent It is widely used in industry and has an irritant effect on mucous membranes

Comparison with Upper Respiratory Cancer

In contrast to the increased incidence of lung cancer, there has been no dramatic rise in incidence in other organs exposed to tobacco smoke Malignant tumors of the nasopharynx and larynx are of epithelial origin, and if tobacco is a potent carcinogen for the bronchial mucosa it should be equally effective in the upper respiratory epithelium, with which it is in contact in greater concentration However, no statistical association has been demonstrated between an increased incidence of upper respiratory cancer and increased consumption of cigarettes. The lips and buccal mucosa have also failed to show a significant rise in incidence of malignancy despite the intimate contact with both the smoke and the cigarette tar

According to the National Office of Vital Statistics the death rate from cancer of the nose and accessory organs was 0 3 per 100,000 in 1940 and 0 4 per 100,000 in 1950 The death rate from cancer of the larynx was 1 1 per 100,000 in 1940 and 1 2 in 1950 Experiences of insurance companies and other sources confirm the national statistics and also support the validity of Newsholme's dictum of half a century ago that accessible cancers do not show spectacular increases in incidence In England, Kennaway found that the incidence of laryngeal cancer remained stationary for three decades and observed that the diagnostic approach to this condition had not been improved to any degree during this period Warran, in New Orleans, noted that between 1937 and 1947 the lung cancer rate had increased from 8 to 21 per 100,000, while laryngeal cancer had increased only from 6 to 8 per 100,000

Analogy with Adenoma

The increased incidence of bronchogenic carcinoma in recent decades has been paralleled by the increase in bronchial adenoma Only a few cases of adenoma were reported before 1930. The subsequent improvement

in diagnostic techniques rapidly led to greater recognition, and by 1940 there were at least 100 cases in the literature. Since then the number of diagnosed cases has increased tenfold. Inasmuch as adenoma is a disease of young adults, the increased incidence was not a result of aging of the population or of prolonged exposure to carcinogens, but was due to improved diagnostic methods Many of the cases of bronchial adenoma had been previously diagnosed as tuberculosis, lung abscess, or recurrent pneumonia

The increase in adenoma cases is an excellent illustration of the fallaciousness of assuming that the increased number of diagnosed cases actually represents a true increase in incidence. The long clinical duration of adenoma (up to thirty years) made it possible, in many cases, for the correct diagnosis to be established eventually. In bronchogenic carcinoma the duration of life is considerably less and the opportunities for multiple diagnostic evaluations of the patient are limited. Many cases of lung cancer are still undetected, but as specialized knowledge of this disease is disseminated the number of undiagnosed cases will be reduced. The incidence of the disease will therefore increase because of better diagnoses The necessity for theorizing about exposure to carcinogens as an explanation for the increases is unwarranted

The increased incidence of lung cancer has been linked to exposure to inhalent carcinogens, such as tobacco smoke, because most of the lung cancers originate from the epithelial surface, which is in contact with the alleged carcinogen Advocates of this theory will have great difficulty in explaining the corresponding increase in bronchial adenoma, which arises from sero-mucous glands well below the surface epithelium.

Experimental Studies

With rare exceptions, the experiments to induce lung cancer in animals have been unsuccessful Moller reported the occurrence of squamous cell carcinoma in rats after painting the skin with tar, but the results were challenged by Passey's demonstration of the frequency of extensive squamous metaplasia in the lungs of old rats. Campbell and Wells also noted the frequent spontaneous occurrence of pulmonary tumors in old mice

A variety of chemical carcinogens has been utilized in ingenious ways Coal tar was injected through the chest wall and into the lungs of rabbits and also instilled intratracheally into mice Methylcholanthrene, benzpyrene, and dibenzanthracene were injected directly into the lungs of experimental animals. On occasion, changes suggestive of carcinoma were produced. The first successful production of squamous cell carcinoma of the lung was accomplished by Andervont, who inserted threads coated with dibenzanthracene into the lungs of mice The tumors produced were successfully transplanted into other animals

Using a tissue-transplant technique, Smith induced carcinomas from embryonal mouse lung by implanting the embryonal tissue along with a chemical carcinogen into muscles of adult animals. The lung transplants developed carcinomatous changes and the neoplastic status was established by further transplantation. Horning also succeeded in producing carcinomas by means of a transplant technique.

Despite the intense search for inhalation carcinogens as etiologic agents in lung cancer, the disease has not been produced by inhalation exposure in the experimental animal Nordmann and Sorge exposed 100 mice to repeated inhalations of asbestos dust and reported two instances of carcinoma, but the findings were not generally accepted Campbell exposed mice to sweepings from tarred roads and to tobacco smoke without producing carcinomas Lorenz exposed mice to tobacco smoke for long periods and produced neither lung cancer nor a significant increase in the number of lung tumors in a highly susceptible strain. (The subject of smoking in relation to lung cancer is discussed more fully in a previous section) Potent carcinogenic hydrocarbons instilled into the lungs of animals have almost invariably failed to produce carcinomatous changes in the respiratory epithelium

Pulmonary Adenoma Pulmonary adenomas in mice have been the subject of much experimentation and occur frequently in certain inbred strains In the A strain of mice, these tumors have been found in as high as 77 per cent of virgin females by 16 months of age and in 71 per cent of males by 14 months The morphological appearance is that of discrete, compact nodules composed of cuboidal cells and apparently arising from alveolar walls The adenomas are capable of transplantability and occasionally metastasize to distant organs Application of carcinogenic hydrocarbons intravenously, subcutaneously, or topically increases the frequency of these tumors in proportion to their spontaneous occurrence in the particular strain The uniformity of appearance of the nodules has suggested a viral origin similar to that of mouse breast tumors The experimental data obtained thus far on pulmonary adenomas in mice appear to have little relation to human lung cancer

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III

Pathology

Introduction

Pathological concepts of lung cancer have undergone radical changes since the disease was described by Laennec and by his English contemporaries in the early nineteenth century. The early studies were based on morphological considerations and the terminology was largely dependent on the stage of the disease. Laennec used the terms encephaloid and medullary because of the resemblance of the whitish tumor to the brain. Among the English authors there is found a variety of descriptive terms, including spongoid inflammation, medullary sarcoma, and fungus hematodes.

In 1838 Carswell published his *Pathological Anatomy,* in which was emphasized the primary nature of lung cancer. About the same time Stokes directed attention to the secondary effects of the tumor, such as pulmonary infection, abscess, bronchiectasis, and atelectasis. In the latter half of the century the influence of Virchow's, Rokitansky's, and Metchnikoff's work on cellular pathology was evident in the gradual abandonment of the gross morphological terms and a greater differentiation of primary lung cancer from secondary tumors and other pulmonary lesions. The clarification of the origin of lung cancer from bronchial epithelium was established by Waldeyer.

In the succeeding years many individual cases of lung cancer were reported, but general interest in the subject was limited and its recognition at necropsy was infrequent. Despite this lack of awareness the literature began to accumulate, and in 1912 Adler was able to collect 374 cases, chiefly from abroad. In this country the failure to recognize the disease in its non-metastatic stage was responsible for much of the delay in the dissemination of pathological knowledge. Increasing clinical interest in recent decades has been reflected in more intensive pathologic research in regard to histogenesis, anatomical classification, and mode of spread.

The early contributions to this subject were derived chiefly from the autopsy room, and the material studied usually represented far-advanced metastatic disease. During the past two decades advances in thoracic sur-

gery have made available for study abundant material with less extens lesions As a result, many changes have occurred in our views about t origin and behavior of bronchogenic carcinoma. In addition, caref necropsy studies have demonstrated latent lesions of limited extent unass ciated with clinical manifestations. The data included in our studies ha accordingly been considered under necroptic and surgical categories

TABLE 1 *Necropsy Incidence of Lung Cancer according to Race and Sex (208 Cases)*

	TOTAL NECROPSIES	TOTAL CANCERS	LUNG CANCERS
City Hospital 1920–49			
White male	5,331	561	91
White female	2,202	330	17
Negro male	594	46	2
Negro female	566	30	1
Others—male	34	5	0
N Y C Cancer Institute 1932–49			
White male	944	857	77
White female	538	495	7
Negro male	135	122	9
Negro female	217	192	0
Others—male	7	7	1
	8,568	2,657	208 *

Ratio of Male to Female = 7.1
Ratio of White to Negro = 15:1

* Approximately 8 per cent of total cancers

Analysis of the autopsy data reveals that the racial distribution amon the cases in our series was predominantly white and that the sex distri bution was predominantly male This has been the general experienc among most necropsy reports.

The distribution according to age showed a greater range than is usuall encountered, probably owing to the fact that in large general municipa hospitals patients in the older age groups form a greater proportion of the population

TABLE 2 *Age Distribution of 208 Autopsy Cases*

	CASES	
DECADES	NO	%
31–40	7	3 4
41–50	34	16 4
51–60	73	35 0
61–70	47	22.6
71–80	40	19 2
81–90	5	2 4
91 and over	2	1 0
Totals	208	100 0

The sixth decade showed the highest percentage but the fifth, seventh, and eighth decades also had a high incidence Ninety-three per cent fell between 40 and 80 years of age The average age was 61 9 years In the males, the average was 59 4 years, in the females, 62 2 years The youngest patient was a man of 32, the oldest patients were a white woman of 94 and a white man of 95 There was no significant age difference between the whites and the non-whites Cases in the first three decades were not encountered

Bronchogenic Carcinoma in the First Two Decades

Although the vast majority of cases of bronchogenic carcinoma occur in the middle and later years of life, the disease has also been found in adolescents and in children Its occurrence in the first two decades is most uncommon, however, and on close study of the primary sources many of the cases quoted in the literature do not qualify

The following is a representative analysis of the cases reported as bronchogenic carcinoma in the first two decades The authentic cases in which detailed data were available are listed in Table 3 Origin from congenital cysts was evident in a few cases, in addition to the more common derivation from bronchial epithelium It is of interest that 13 of the 29 cases were adenocarcinomas, of which 9 occurred in males and 4 in females

In a series of 1 888 cases of bronchogenic carcinoma, Fischer found 4 in the first decade and 18 in the second decade Simons found 1 in the first decade and 6 in the second in 2,796 cases In their compilation of 4,307 cases, Ochsner and DeBakey described 5 in the first decade and 31 in the second Loizaga found 1 in the first decade and 4 in the second in a series of 183 necropsied cases He also cited 3 additional cases in adolescents reported by Krompecher, Huguenin and Masto, and Polak, respectively In Adler's classic treatise there are 6 cases under 20 years of age mentioned

Several cases quoted in the literature either are doubtful or are definitely not carcinomas Two cases of Huguenin are doubtful In the first, a male of 18, Huguenin did not make a positive diagnosis and stated that although he was suspicious of carcinoma, it may have been a granulomatous lesion His second case, a boy of 14, both he and Ameuille interpreted as an anaplastic carcinoma rather than mediastinal lymphosarcoma, which it closely resembled

The patient of Rolleston and Trevor, a girl of 13, was diagnosed as a sarcoma Several features suggest the possibility that the condition was an undifferentiated bronchogenic carcinoma with contiguity invasion of the ribs Adler listed Aschenborn's case, which was not confirmed histologically, although the autopsy findings are compatible with primary bronchogenic carcinoma McAldowie was credited by Frissell and Knox and Beardsley with reporting probably the first case, in 1876, a child 5½ months old

TABLE 3 *Bronchogenic Carcinoma in the First Two Decades*

AUTHOR AND YEAR	RACE	SEX	AGE	SITE	METASTASES	HISTOLOGY	REMARKS
Coats 1888	W	M	17	RLL	Tracheobronchial, aortic, mesenteric LN, femurs, ribs, vertebrae, pancreas, liver, peritoneum, brain	Colloid and mucus producing adenocarcinoma	Interpreted as mucous gland origin, probably from segmental bronchus
Werner 1891	W	F	19	RLL	Both lungs, draining LN, liver, spleen, kidneys	Small cuboidal cell carcinoma	
Papinio 1893	W	F	12	RML RLL	One axillary node	Probably carcinoma	
Hall and Tribe 1905	W	M	17	LLL	LUL, retroperitoneal and axillary LN, skull	Columnar cell carcinoma	Probably from main or lower lobe bronchus
Horn 1907	W	F	18	LMB	Few hilar glands	Ciliated cylindrical cell carcinoma	Suggests origin from bronchial adenoma
Letulle 1924	W	M	20		Widespread	Squamous cell carcinoma	In a case of heredosyphilis and bronchiectasis
Hirsch and Ryerson 1928	W	M	6	RLL	Draining LN, left lung, RUL, thymus, left tibia	Adenocarcinoma	
Schwyter 1928	W	F	1¼	LL	Tracheobronchial LN	Adenocarcinoma	
	W	F	5 mo	RL	None	Squamous cell carcinoma	In congenital cyst lined by non-malignant cylindrical and malignant squamous cells
Simpson 1928–29	W	M	13	RL	Numerous	Carcinoma	
Simons 1931	W	M	19	RLL RML	Bronchial, tracheobronchial, and mediastinal nodes, ribs, left lower lobe, spleen(?)	Adenocarcinoma	Histology by E. T. Bell
Beardsley 1933	W	F	1 yr 5 mo	LL	Absent	Mucus-producing adenocarcinoma	Apparently peripheral type

Kilduffe and Salasin 1933	W	M	14	RLL	Mediastinum	Alveolar carcinoma	
Sommer 1934	W	F	7	RLL RML	None	Ill-defined adenocarcinoma	Limited autopsy Interpreted by E T Bell as probably arising in congenital cyst
Gould 1934	W	M	10	RLL	None	Carcinoma grade III	
Lereboullet *et al* 1935	W	F	5	RL	None	Oat-cell carcinoma	
Adamson *et al* 1936	W	M	19	RLL	Pericardium, heart, pancreas, kidney, adrenal, mesentery, vertebrae, ribs, sternum	Anaplastic carcinoma	Origin from lobar bronchus
Cardelle *et al* 1936	B	M	11	LLL	Intrathoracic	Oat-cell carcinoma	Origin from lobar bronchus
Frissell and Knox 1937	B	M	17	RUL	None	Malignant papillary adenoma with local invasion	
Wasch *et al* 1940	B	M	18		Extensive visceral	Adenocarcinoma	Duration of 7 years after diagnosis first made
Hauser 1942	B	F	1 yr 5 mo			Small cell carcinoma	
Field 1943	W	F	4 yr 4 mo	RL	Homolateral intrathoracic nodes, right axillary LN, right lower cervical LN upper retroperitoneal LN	Anaplastic carcinoma	Suggestive of peripheral origin with extensive contiguity invasion of chest wall
Mulligan and Harper 1943	W	F	19	RML		Squamous cell carcinoma	Incidental autopsy finding
Jones *et al* 1943–44	W	M	13	RL	None	Papillary growth with basal cells glandular elements and local invasion	Malignant bronchial adenoma
Halpert and Russo 1944	B	M	10	RML	Both pleurae, tracheobronchial LN, kidneys, ribs, vertebrae, heart	Anaplastic carcinoma	
Dick and Miller 1946	W	F	9	BMB	Femur	Anaplastic carcinoma	
Kirsch and Colat 1949	W	F	14	LL	Right axillary	Anaplastic carcinoma	Extensive necrosis of tumor
Twaite 1951	B	M	12	LLL		Adenocarcinoma	Extensive thrombosis and necrosis
Cayley *et al* 1951	—	F	13	LL	Right lung, post mediast, left pleura, left diaphragm intercostal muscles both breasts, bones	Large cell undifferentiated	

Like Aschenborn's case, the data are compatible with bronchogenic carcinoma but lack histological confirmation. McAldowie stated that Ebermann had observed one patient age 9, and Bennett one aged 11 years Bennett's patient had an intrathoracic but not a pulmonary tumor. Curran's case, a boy of 10, is very obscure and the histology proved unsatisfactory.

The five cases reported by Duguid were in a series of intrathoracic tumors, and it is not clear whether they form part of the 71 bronchogenic carcinomas confirmed histologically The series of Davidson, also frequently quoted, likewise included all types of intrathoracic new growths. His two patients under 21 years had mediastinal and thymic lymphosarcoma The patient of Weille-Halle and his co-workers was a child of 1 year with mediastinal sarcoma. The cases of Cathala and Ducas are not carcinomas Case 1 was diagnosed embryonal carcinoma from a metastatic lesion, origin from the lung being based on the clinical features Case 2 was diagnosed lymphosarcoma because of the changes in an axillary lymph node. Autopsy was lacking in both instances. Cruchet and Dupuis' case also was a lymphosarcoma The case of Gauducheau and Tardiveau and Case 1 of LeLourd and Clarac appear to be similar. The second case of the authors last mentioned has insufficient data on which to base an opinion

General Considerations

The data on the pathology of carcinoma of the lung were obtained from the study of 208 autopsies and 69 resected lungs They indicate that in all respects carcinoma of the lung acts much as other carcinomas, conforming to known facts about malignant disease in general. It follows the laws of development for normal conditions, modified by the influence of environment on the intensity of its growth.

Histogenesis

Carcinoma of the lung arises from the epithelium of the bronchial tree at any point from the main bronchus to the respiratory bronchiole. The various histological features encountered can be understood best if the normal character of the epithelium and the changes that may take place are borne in mind The larger bronchi are lined chiefly by ciliated cylindrical cells interspersed with goblet cells and have undifferentiated basal cells from which the first two develop. The bronchioles are lined by nonciliated cuboidal cells Squamous metaplasia is a common phenomenon in the larger bronchi Goblet cell metaplasia in the smaller radicles is encountered in autopsy material almost as frequently as the squamous metaplasia upon which attention has been focused The potentialities of the cell and the degree of differentiation or lack of differentiation govern the histological character of the carcinoma They also explain the marked pleomorphism



FIG 1 *Hilar Squamous Cell Carcinoma of Right Middle and Lower Lobar Bronchi* The right middle and lower lobar bronchi are stenosed and surrounded by malignant tissue The bronchial tree distal to the stenosis is greatly dilated to the pleura and filled with purulent exudate The bronchiectasis had caused an empyema The hilar nodes are involved by metastases.



FIG 2 *Hilar Undifferentiated Carcinoma of Right Upper Lobar Bronchus* The right upper lobar bronchus is stenosed (upper) by a mass of white, soft tumor tissue of fish-flesh appearance Beneath large tumorous lymph nodes (lower) there is visible the superior vena cava and the upper portion of the right auricle The tumor tissue compresses the vena cava and occludes it by cancerous thrombosis.

so frequently seen The mucous glands need not be implicated as a site of origin, and actually the reported cases are very questionable

Anatomical Classification The anatomical classification of carcinoma of the lung is based on the fact that the natural course of the disease is governed largely by the site of origin of the tumor. On this basis lung cancer can be divided into three groups 1 Hilar, 2. Midzonal, 3 Peripheral.

The hilar group includes tumors that arise from the main bronchi, the lobar bronchi, or the segmental bronchi at or near the mouth (Figs. 1, 2, 3) The midzonal group includes tumors that arise from the bronchi or bronchioles at some point peripheral to the origin of the segmental bronchi and at some distance from the pleura. The peripheral group is subpleural and arises from the smallest bronchi or bronchioles (Fig 4).

In autopsy material, the site of origin may be difficult or impossible to determine but in the majority of cases, it can be stated with presumptive accuracy. The data in 206 autopsies are given in Table 4 and Figure 5



Fig 2. *Continued*

The site of origin could not be determined in two cases One was discovered during the histological examination of routine material, and it could only be established that it arose in a large bronchus There were no metastases that might have given the clue to the side affected. The second patient was subjected to pneumonectomy at another institution, and the available data were insufficient for anatomical classification

The hilar group predominated and included 83 5 per cent of the cases. The peripheral group was about 10 per cent and the midzonal more than 5 per cent There was no predilection shown for either lung The upper lobes were more frequent sites of origin than the lower The surgical material is by its very nature a restricted group However, practically the same percentage, 79 per cent, were hilar in site The remainder were midzonal The peripheral group was not represented

TABLE 4 *Anatomical Classification of 206 Carcinoma*

	RUL	RML	RLL	RML RLL	RL	LUL	LLL	LL	TOTAL	[illegible]
Hilar	42	4	12	3	23	39	16	33	172	[illegible]
Midzonal	7	0	3	0	0	2	1	0	13	[illegible]
Peripheral	4	0	2	1	1	9	2	1	20	[illegible]
Unclassified	1 bilateral								1	[illegible]
Totals	54	4	17	4	24	50	19	34	206	[illegible]

Histological Classification. The histological classification of carcinoma of the lung is necessary because the natural course of events in the disease is influenced to some degree by the type of cell growth. Pleomorphism may be so marked that classification of an individual case may be difficult, but



FIG 3 Pneumonectomy specimen showing small tumor arising from left lower lobe bronchus and extending into the tertiary bronchi

the majority of cases have a predominant type of cell which permits placing in a specific group. Cell types are classified into four groups: (1) Squamous, (2) Adenomatous, (3) Undifferentiated, (4) Mixed.

In the autopsy series, the squamous type was the most numerous, comprising slightly more than half the cases (Fig. 6). The adenomatous (Figs. 7A-B-C) and undifferentiated types (Fig. 8) occurred about half as frequently. Rarely a case showed such an admixture of cell types that it could only be placed in the mixed group (Fig 9). The data are summarized in Table 5:

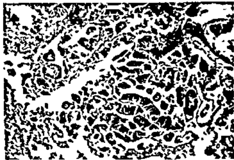


FIG 7A Adenocarcinoma with site of origin in main bronchus at the mouths of the lobar branches It is characterized by a tall opaque nonciliated non-mucus-producing epithelium.



FIG 7B Adenocarcinoma with site of origin in a segmental bronchus The cell is columnar and mucus producing The extension into the alveolar spaces reproduces the appearance of the 'alveolar cell' carcinoma of the lung

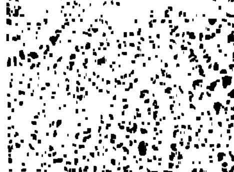


FIG 7C Adenocarcinoma resembling the lobar type of 'alveolar cell' carcinoma The site of origin was the left lower lobar bronchus, the lower lobe was homogeneous and resembled lobar pneumonia All the alveoli are lined by tall columnar cells There is some tendency to papillation The alveolar walls are normal, and the alveolar spaces contain mucus

and adenomatous tumors, 1 in 8 would be so located The peripheral tumors of undifferentiated nature were rare

The resected lungs included a much greater predominance of squamous carcinoma, 70 per cent being of this character, whereas 20 per cent were adenomatous, 7 per cent undifferentiated, and 3 per cent mixed in nature

'ALVEOLAR CELL' TUMOR

The so-called 'alveolar cell' tumor of the lung has formed a field of interest and contention ever since this type of carcinoma was reported by Malassez and Musser The histological features that have been mentioned as characteristic of this carcinoma are the eosinophilic nonciliated columnar or cuboidal epithelium lining alveolar spaces in one or more layers, the

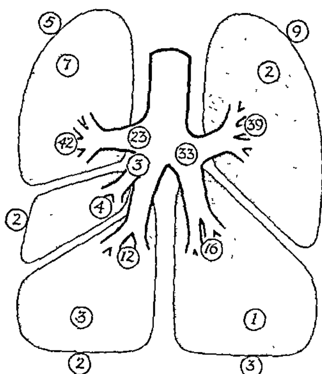


Fig 5. *Diagram of Site of Origin of 206 Necropsied Cases Showing Preponderance of Hilar Lesions*

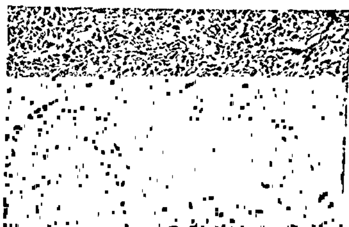


Fig 6 *Squamous Cell Carcinoma* The cells are well differentiated although not keratinizing Many nests completely fill the alveolar spaces

tremely difficult to demonstrate with certainty, especially in autopsy material It may be stressed at this point that our success in tracing origin to the bronchioles rested upon serial sectioning of lesions barely visible to the naked eye or barely palpable to the examining finger, and on the study of

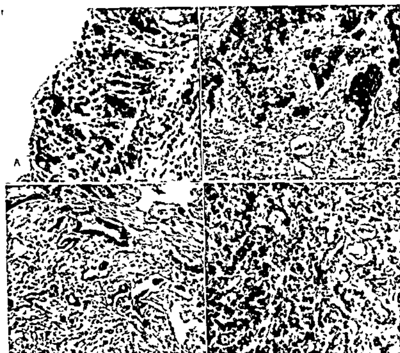


FIG 9 *Pleomorphism in Bronchogenic Carcinoma* The surface epithelium (A) shows a change to a high columnar eosinophilic cell, penetrating down through the wall Another area (B) has a typical squamous character A third area (C) has tubular or glandular structures with tall opaque cells A fourth area (D) has a mixed structure of cords and tubules or glands The eosinophilic character of the cells gives this area the appearance of a mixed carcinoma of the liver All these fields are found in the same slide

portions of the lung which seemed uninvolved by tumor. It was in this material that the least extensive lesions were discovered Serial sectioning of minute lesions was essential in order to obtain accurate information regarding histogenesis of the tumor

'Alveolar cell' carcinoma of the human lung has a striking morphological resemblance to pulmonary adenomatosis or jaagsiekte of sheep In this disease there is the same tendency for the alveoli to be lined by cells of the 'alveolar' type, but involvement of the bronchiolar epithelium and metas-

tendency to papillation, exfoliation, and formation of giant cell masses, the production of mucus, and the freedom of the bronchiolar epithelium from neoplastic changes. Two opposed views have been advanced in regard to its histogenesis. One school supports the concept of origin from an epithelial cell lining the alveolus. The other school holds that the origin is from bronchiolar epithelium that has grown down into the alveolus.

In our material, 9 cases of this type of carcinoma were encountered, 4 among the autopsies and 5 among the surgical specimens. In 8 of the 9 cases the tumor was traceable to bronchial epithelium.



FIG 8 *Undifferentiated Carcinoma* Undifferentiated cell carcinoma of the bronchus The cells bear a close resemblance to lymphoid elements. The tumor can be distinguished from lymphosarcoma by the use of the reticulum stain, the sarcoma having a reticulum network which is absent in the bronchogenic tumor.

The type of cell is an unreliable criterion for site of origin The eosinophilic cell is encountered in other bronchogenic carcinomas, although it may not be a predominant feature as it tends to be in the 'alveolar' tumor. One of our tumors of mixed histology showed a malignant surface epithelium of this nature. Cheek and Muirhead reported a bronchial adenoma producing an 'alveolar cell carcinoma' pattern. During the extension of tumor through the lung, frequently alveoli are lined by tumor cells in single or multiple layers and may display papillation, particularly if the tumor is adenomatous The production of mucus can occur with any adenocarcinoma Individual areas where mucus is abundant will closely mimic the 'alveolar cell' tumor. A perfect example of these various features was displayed in a resected lung: the tumor arose from the anterior segmental bronchus of the upper lobe and had an admixture of squamous elements, adenocarcinoma, and, in addition, the features of 'alveolar cell' tumor.

Freedom of bronchiolar epithelium from neoplastic change may be ex-

usually attributed to embolization from a primary focus to other parts of the same or opposite lung through the lymphatic or venous channels. When the bronchioles are the site of origin (Fig 10), a surprising tendency to be multicentric is evident (Fig 11). It may be limited to a lobe or a lung, or be bilateral One of the autopsied cases had a bilateral origin which resulted in the gross anatomical features of a bronchopneumonia. Four of the resected lungs showed multicentric lesions The same feature of multicentricity is evidenced in origin from other parts of the bronchial tree One case



FIG 10. Bronchiologenic carcinoma resembling the bronchopneumonic form of 'alveolar cell' carcinoma

had tumors arising from several branch bronchi and one segmental bronchus Another had the superior and lateral basal segmental bronchi in a lower lobe A third case showed a metastasizing tumor arising from the main bronchus and multiple noninvasive carcinomas throughout the upper lobe. All of these tumors were squamous carcinomas

The site of origin does not necessarily govern the histological type of carcinoma that develops, although there are certain tendencies in different radicles of the bronchial tree In the autopsy material, the various types arose from all parts of the bronchial tree, from the main bronchus to the bronchioles The adenocarcinomas and the mixed adenomatous and squamous carcinomas originated more frequently in the segmental and smaller bronchi, comprising approximately 50 per cent of the lesions involving these bronchi. In the resected lungs there were fewer adenomatous lesions in the segmental bronchi However, the tendency for this histological type to develop in the branch bronchi and bronchioles was very evident.

One other type of bronchogenic tumor deserves consideration. An example

tases are absent The disease is presumed to be viral in nature The resemblance does not imply, however, that the human cancer is also viral, for it must be borne in mind that different etiologies may produce the same histological manifestations

Sex and Age Distribution of Histological Types

The sex distribution of the histological types among 208 autopsies was predominantly male. The only finding of importance was the relatively high incidence of adenocarcinoma among females. Whereas over 90 per cent of the squamous and undifferentiated tumors occurred among men, 32 4 per cent of the adenocarcinomas were among the females and included more than half, 58 per cent, of the cases in this sex. In the surgical cases, the same tendency for the adenocarcinomas to appear among the women was evident Of the 9 women, 6 had adenocarcinomas The 60 men developed 8 adenocarcinomas, 13 per cent.

The age range in the autopsy series was wide in all groups. Among the squamous cell carcinomas, the youngest patient was 38 and the oldest 80 years. One of the mixed type, having both squamous and adenomatous features, occurred in a 95-year-old individual. The adenomatous type showed practically the same age range, 44 to 94 years The youngest example of undifferentiated carcinoma was a person aged 32, the oldest one aged 87

The age distribution of the three types revealed only one observation of interest, the high average in squamous carcinoma among women. The average age in the squamous group was 62; among the men 59 9, and among the women 67.3 In the two other groups, the difference between the sexes was insignificant In the adenocarcinomas the average age was 60 years, in men 58.8, and in women 60 2 Almost identical figures were found in the undifferentiated group, the average 60 years, men 60, women 63 3 Age does not appear to be a prime governing factor in the histological types.

Site of Origin

The site of origin of the hilar tumors showed a predilection, judged from the autopsy material, for the lobar branches or the distal portion of the main bronchus, regardless of the histological type Among 206 autopsies in which the site could be judged with reasonable accuracy, about 55 per cent of the tumors arose from the lobar bronchi, 30 per cent from the main bronchi, and 15 per cent from the segmental or smaller radicles The resected lungs showed a different distribution. In 66 cases in which the site could be determined, 36 of the tumors arose from segmental bronchi, 15 from lobar bronchi, 13 from branch bronchi or bronchioles, and 2 from the main bronchus

The majority of tumors are unicentric in origin Multiple tumors are

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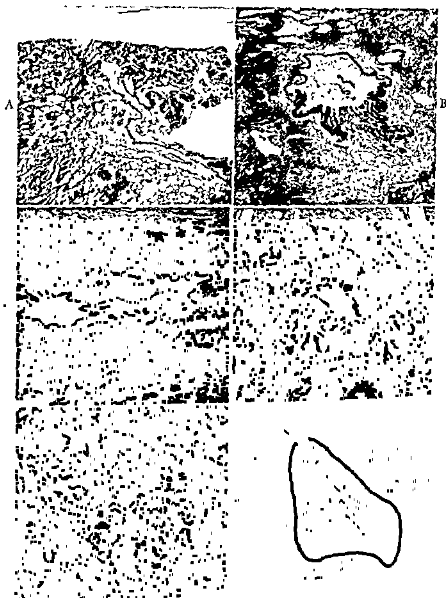


FIG 11 *Multicentric Bronchogenic and Bronchiologenic Adenocarcinoma of the Left Lower Lobe* All the lobe except the anterior basilar broncho-pulmonary ... and tending

bronchus was narrowed. The entire broncho-pulmonary segment was ... confluent tumor tissue extending to the pleura The anterior basilar segmental

(Continued on facing page)

bronchus and its branch bronchi appeared slightly dilated but otherwise normal In the parenchyma there were two small tumor masses

Microscopy The tumor is characterized by a tall nonciliated eosinophilic cell displaying a marked tendency to papillation and showing origin from bronchial epithelium

A The tumor occluding the branch bronchus of the posterior basilar segment (cross hatched area in diagram) shows sharp transition from columnar epithelium to the papillomatous growth and extension into the adjacent alveoli, where a moderate amount of mucus is present

B A more distal area from the broncho-pulmonary segment of the same branch bronchus as A shows a small bronchus with transition from normal to malignant epithelium

C A subpleural area in the lateral basilar broncho-pulmonary segment The pleura is thick and fibrous The alveoli lying adjacent to and incorporated in the area of fibrosis show a similar transition between low cuboidal bronchial epithelium and malignant eosinophilic cells tending to form small papillary projections,

D A lesion adjacent to a thickened interlobular septum of the medial broncho-pulmonary segment A small bronchiole is lined by tall normal epithelium changing to tall neoplastic cells extending into and lining alveoli surrounded by fibrous tissue

E A lesion in the anterior basilar broncho-pulmonary segment showing the transformation of the normal epithelium of a respiratory bronchiole to the neoplastic type with papillation and extension into the associated alveoli

The second branch bronchus of the posterior basal segment has a lesion which duplicates that illustrated by A

The examination of the anterior basilar broncho-pulmonary segment is particu-
larly illuminating The segmental and branch bronchi are normal Many micro-
copic foci, usually not visible to the naked eye, sometimes barely palpable, are
resent throughout the parenchyma They show origin from respiratory bronchi-
les as illustrated in E The associated alveoli are lined by malignant cells Some
oci contain mucus, some do not Only serial sectioning demonstrates connection
th the bronchiole, individual sections from the same block frequently show
ly alveoli lined by tumor cells and present the microscopy of the 'alveolar cell'
mor as illustrated and recorded in medical literature The parchenyma sur-
nding these microscopic tumors is normal
All the tracheobronchial nodes resected have tumor foci of adenomatous pat-
and eosinophilic cells Mucus is scanty or absent

was encountered in a lobe resected for chronic bronchiectasis This association has been met by other investigators It has been reported in the literature under such terms as 'minute peripheral pulmonary tumors' and 'peripheral bronchial adenoma' (Fig. 12). As the terms imply, the site of origin is in the smaller bronchi and bronchioles, and the location is pe-



Fig 12. *Peripheral Bronchial Adenoma*

A In the wall of a small branch bronchus there is a nest of homogeneous, small, darkly stained epithelial cells which extend down into a smaller segment

B Slightly beyond the areas shown in Fig A there is penetration of the tumor cells into channels, apparently lymphatics of the mucosa. The cells are small, homogeneous in size, shape, and staining, and have dark round or oval nuclei Mitoses are absent The groups of cells are separated by thin fibrous strands which carry small blood vessels

ripheral. It tends to be multicentric in origin. The histological examination shows intramural tumors consisting of small homogeneous cells with obscure cell boundaries and small, round, evenly stained nuclei usually failing to display hyperchromatism, nucleoli, or mitoses. They closely resemble carcinoids. Usually they are confined by the basement membrane. Occasionally small masses of the cells are found in the tissues surrounding the bronchus Associated inflammatory reaction is usually absent The relation of this tumor to carcinoma remains debatable. Many observers are in agreement with Prior, who holds they are benign in nature and have no tendency to become malignant Umiker and Storey, however, reported a case that developed invasive carcinoma after having been under observation for five

years. The possibility that this tumor may represent a carcinoma of very low grade malignancy must be given serious consideration

Course of Events

The course of events is governed by the anatomy of the lung, the site of origin of the tumor, and the histological character of the cell The lung is an organ extraordinarily rich in vascular and lymphatic components, which govern the routes for metastatic lesions The site of origin—hilar, midzonal, or peripheral—has inherent sequelae The distortion of the bronchial lumens and walls leads, in the hilar and midzonal tumors, to atelectasis and infection of the related bronchopulmonary segments The peripheral tumors have their main effects in adjacent extrapulmonary tissues The squamous and adenomatous cells tend to be centrifugal in their direction of growth, the undifferentiated cells are predominantly centripetal.

The earliest change in the gross appearance—seen most clearly in hilar tumors and most frequently in resected lungs—is granularity and thickening of the mucosal surface The color is light brown-yellow. When the lobar or more distal bronchi are involved there is distinct stenosis The midzonal tumors may be difficult to trace to their origin in the bronchial tree. If they are seen at an early stage the same features of granularity and stenosis found in the hilar group are evident Usually, however, the tumor is globular, the site of origin difficult to demonstrate, and the bronchial tree of the adjacent segments displaced outward by the expanding growth Tumors of multicentric origin, especially those arising from bronchioles, may mimic bronchopneumonia, tuberculosis, or Friedlander infection Cavitation occurs from central necrosis within the tumor This change apparently is more frequent in the squamous tumors The peripheral type tends to become adherent to adjacent tissues, and here likewise difficulty is encountered in tracing the origin to bronchial ramifications.

Spread of Tumors

Carcinoma of the lung spreads by four routes: (1) bronchogenic, (2) contiguity, (3) lymphogenous, and (4) hematogenous

Bronchogenic Noninvasive carcinoma occurs in many organs It is recognized in the cervix, endometrium, vulva, stomach, skin, kidney, breast, and other tissues It displays the ability to spread over adjacent surfaces, confined above the basement membrane In the lung it has been encountered *infrequently In our series there was one case among the autopsies and two* among the resected lungs (Fig 13) They were all squamous carcinomas The concept of surface extension, however, explains many features found in carcinoma of the lung The squamous and adenomatous tumors tend to be centrifugal in the direction of growth Spread toward the hilum occurs

but apparently at a slower rate. They are malignant cells that have great growth potentiality and partial differentiation. In this respect they are similar to the cells found in other organs which spread along the surface. A spread along the mucosa down into the alveoli would explain the frequent observation of alveoli lined by tumor cells It would likewise explain the appearance of the 'alveolar cell' tumor These tumors are usually bronchiologenic in origin. They lie at the entrance of the atrium The tendency of the cell to extend outward would naturally line the atrium and alveoli (Fig. 14).

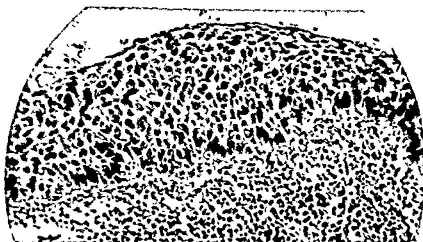


FIG 13 *Noninvasive Squamous Cell Carcinoma* Noninvasive stage of squamous cell bronchogenic carcinoma.

The metaplasia of the epithelium in the small radicles of the bronchial tree, as noted previously, is more frequently to a mucus-producing cell, rather than to the squamous cell seen in the larger radicles This would explain the mucoid appearance encountered so frequently in this type of carcinoma This concept also offers an explanation of our observation that a high percentage of tumors arising in branch bronchi and bronchioles were adenomatous in character.

Aspiration implantation carcinoma is theoretically possible. Apparently viable tumor masses are frequently found in alveoli peripheral to the tumor and even in nontumorous lobes of the same or opposite lung. Furth succeeded experimentally in producing carcinoma of the lung by implantation but it has not been proved in human material

Contiguity In contiguity invasion, the normal confining structures of the lung are penetrated Their structure and response to the foreign cells determine the course of events. In the squamous cell tumor, a marked desmoplastic response is frequent Locally, the tumor surrounds arteries, veins, lymphatic channels, and lymph nodes It may penetrate into adjacent organs,

such as vertebrae, pericardium, heart, trachea, esophagus, or chest wall. Extrapulmonary contiguity invasion is most striking in the peripheral tumors. Of the 20 peripheral tumors in the autopsy series, 8 showed extensive invasion of the chest wall, ribs, and vertebrae, and 1 encased the spinal dura The trachea and esophagus were found completely surrounded in 1 case. In the hilar group, the superior vena cava was compressed in 9 instances and penetrated in 2 cases. The right-sided tumors are more likely to result in caval obstruction One case had origin in the left lower lobe.



FIG 14 *Terminal Bronchiologenic Carcinoma* The bronchiole is partially-lined by columnar epithelium which changes to a neoplastic type showing anisocytosis, macronuclei, and hyperchromatism An adjacent alveolus is filled with malignant cells

Lymphogenous The lymphatic system of the lung is extremely rich and complex Its invasion leads to true metastases, which follow the course of the current A clear concept of the lymphatic system of the lung is necessary to understand the sites at which metastases may appear. The lymphatic system does not extend beyond the alveolar duct; it is absent around the atrium and alveolus It consists of two elements, a superficial pleural and a deep parenchymal The deep lymphatics are the bronchial, the periarterial, and the perivenous The bronchial and periarterial channels drain toward the parenchyma The perivenous lymphatics drain toward the hilum, except close to the pleura In this region they follow the septal and pleural veins and flow toward the pleura, draining to the hilum through the superficial pleural channels. Anastomosis between the channels within the parenchyma

is rich, especially at the region of the respiratory bronchiole and alveolar duct. Anastomosis between the deep and superficial systems occurs in a narrow subpleural zone, but the flow is only outward to the pleura because the valves of the lymphatic channels, present in the superficial system, prevent a back flow toward the parenchyma. The valves do not prevent free communication between the pleural lymphatic channels themselves Involvement of the lymphatic channels may be followed by embolization or permeation. Embolization is favored by the mobility of the lung and can occur either in a more distant channel or in a draining lymph node. The small caliber of the vessels and the low pressure of the current favor permeation Even with nodal involvement the lymphatic system remains a protective mechanism One of the functions of a node is to act as a trap for foreign material Malignant cells will not extend beyond it until it has been destroyed, its efferent channels have been involved, or it has been by-passed by another lymphatic channel.

Hematogenous The vascular bed of the lung is as rich and complex as the lymphatic system. Its invasion leads to both intrapulmonary and extrathoracic metastases. The involvement of veins is common, and the size of the tumor has no definite bearing on its occurrence. Veins are thin-walled structures which offer little resistance to extension of tumor growth They are easily penetrated and are particularly susceptible near the sites of origin because of the diminishing sturdiness of the wall with its diminution in size. Because the malignant cells at this point are penetrating into a vessel whose current is passing from a small caliber to a larger caliber, embolization (Fig 15) is easily accomplished and may as readily be extrathoracic as intrapulmonary Thrombosis by a neoplastic mass and propagation through the venous channel can occur In the larger veins, the thrombosis is a sequel of contiguity invasion of surrounding tissues The superior caval system and the veins at the hilum are the most susceptible. The superior cava is at first stenosed and then thrombosed, the thrombus almost invariably being malignant. It can extend in one of two directions, either down toward the auricle or up into the tributaries. In our autopsies, stenosis occurred in nine cases, in two cases followed by tumor thrombosis. Twice the cancerous thrombus affected the azygos veins and once the innominate vein Two cases had extension into the right auricle. Large pulmonary arterial emboli were present in two instances.

The large pulmonary veins were found occluded by cancerous thrombi in 12 instances, the tumor once presenting into the left auricle. Microscopic tumor emboli were present in the coronary circuit in one case

Erosion of the veins may occur and cause exsanguinating hemorrhage Although not encountered in this series, it was subsequently observed in two other cases A subintimal venous involvement by tumor may be present This method of spread is extremely rare and was not encountered.

Arterial malignant thrombosis occurs with much less frequency than the venous It was encountered in five cases among the autopsies All the tumors were hilar in site Two were squamous and three were adenomatous In one case tumor emboli were present in the lung beyond the carcinomatous thrombus



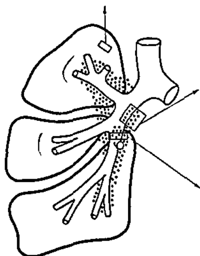






FIG 15 *Intrapulmonary Carcinomatous Venous Embolism* Lower lobe tumor with unsuspected upper lobe involvement.

Sites of Metastases

The most frequent site of metastasis is the draining lymph nodes, followed by liver, adrenal, kidney, bones, brain, heart, and spleen. True metastases were present in 190 cases and are listed in Table 6:

Table 6 *Metastases in 208 Autopsies*

Lymphatics	Tracheobronchial	167		Clavicle	1
	Mediastinal	57		Femur	1
	Cervical	27		Humerus	1
	Axillary	12		Unspecified	3
	Abdominal	56		Diffuse bone marrow	1
	Pelvic	4	Cardiovascular system	Pericardium	23
	Inguinal	1		Myocardium	13
Viscera	Liver	71	Gastro-intestinal system	Peritoneum	8
	Adrenal	54		Omentum	1
	Kidney	37		Small bowel	4
	Spleen	15		Large bowel	1
	Pancreas	7	Nervous system	Dura	9
Bones	Ribs	35		Brain	21
	Vertebrae	25		Spinal cord	2
	Pelvic girdle	8	Skin and muscles	Voluntary muscles	10
	Skull	4		Skin and subcutaneous tissue	5
	Sternum	3			

Lymphogenous metastases predominated, being found in 177 instances. The hilar lymph nodes were almost always affected and frequently the upper abdominal and mediastinal nodes. The cervical nodes were fairly frequently involved and occasionally the nodes of pelvic and inguinal chains

Among the visceral organs the liver, adrenal, and kidney were the most frequent sites of metastases The spleen, ordinarily thought to be an unusual organ for secondary tumor, was involved in 8 per cent. The heart also was fairly frequently affected

In the osseous system, the thoracic cage and vertebrae were the usual sites. There was homolateral rib involvement usually. The figures on the long bones are probably too low, for they were seldom examined unless the history indicated a specific site, and post-mortem roentgenological studies were not carried out.

The same statement applies to the cerebral metastases Only 62 brains were obtained, of which one-third had metastases They are summarized in Table 7.

Table 7. *Cerebral Metastases*

	PRESENT	ABSENT	TOTAL
Squamous	13	21	34
Adenomatous	2	9	11
Undifferentiated	4	11	15
Mixed	2	0	2
Total	21	41	62

Contiguity invasion only, without demonstrable metastases, was present in seven instances This isolated method of spread was usually seen in peripheral tumors and showed extensive invasion of chest wall, cervical tissues, mediastinum, or vertebrae A few were central tumors arising in lobar bronchi and enclosing the mediastinum, esophagus, trachea, aorta, and base of pericardium

Eleven cases were local tumors free of metastasis They sometimes showed local contiguity invasion

The metastatic tumor usually, but not invariably, duplicated the parent neoplasm One mixed tumor, having both squamous and adenomatous components, showed a squamous metastasis to the brain Another case, an undifferentiated carcinoma, had a mucus-producing metastasis in the kidney A third case, squamous in nature, produced a mixed squamo-adenomatous cerebral metastasis This type of metastasis seems to reflect the pleomorphism so frequently displayed by bronchogenic carcinoma

The method of metastasis was seldom confined either to the lymphogenous or to the hematogenous routes The undifferentiated tumors displayed a greater predilection for the lymphatic route of metastasis Usually both routes were used Among the squamous tumors, about half had both lymphogenous and hematogenous metastases In the adenomatous group there were about two-thirds, and in the undifferentiated carcinomas about three-fourths Isolated lymphatic metastases in each group numbered about one in three, the squamous being slightly more prevalent than the others Pure hematogenous metastases were uncommon Frequently, the metastases were combined with contiguity invasion

Complications

Intrathoracic complications are frequent, usually due to infection, and largely confined to the hilar group Those found in the autopsies are listed in Table 8

TABLE 8 *Nontumorous Intrathoracic Associated Conditions*

Pleural effusion	15
Bronchiectatic abscess	70
Bilateral bronchiectasis	38
Homolateral bronchiectasis	40
Empyema	9
Serosanguinous pleural effusion	7
Lobar pneumonia	3
Acute endocarditis, myocarditis, or pericarditis	27
Serosanguinous pericardial effusion	3
Tuberculosis	11

…e most common change encountered was infection of the broncho-…nary segments It was most severe distal to the tumor, where it had

produced the changes of recurrent unresolved pneumonias or eventuated into bronchiectatic abscess This type of cavitation had to be distinguished from cavitation secondary to central necrosis in tumor tissue, a common observation in large tumors Nontumorous lobes frequently had less severe chronic bronchiectasis, especially when the tumor was in the upper lobe Frequently the bronchiectasis was bilateral

Clear pleural effusion was encountered more frequently than serosanguinous It tended to be loculated rather than diffuse. The hemorrhagic fluid appeared to be a late rather than an early manifestation, especially in hilar tumors.

The most satisfactory classification of bronchogenic carcinoma is one based on both the anatomical site of origin and the histological character of the growth Anatomically, they are divisible into hilar, midzonal, and peripheral Histologically, they are squamous, adenomatous, and undifferentiated, a few may be called mixed, when no specific histological type predominates The great majority fall into the hilar group, of which half or more are squamous Any histological type may arise in any part of the lung. The undifferentiated tumors display a greater predilection for origin in the hilar region than the other two types. The adenomatous tumors are relatively more frequent in the midzonal group and among females. The site of origin of the hilar group is usually a lobar bronchus or the main bronchus in the neighborhood of the mouths of the lobar bronchi A few arise from the mouths of the segmental branches The midzonal group arises from small bronchi or bronchioles beyond the mouths of the segmental branches. The peripheral group is subpleural and arises from small bronchi or bronchioles. They are usually unicentric in origin and occasionally multicentric. The bronchiolar tumors are frequently multicentric in origin

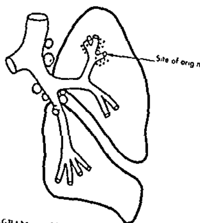
The course of events is governed by the anatomical structure of the lung, the anatomical site of origin, and the histological character of the growth The tumors are spread by contiguity invasion, directly through the bronchial lumen, through the lymphatic channels, and by way of the blood stream. Aspiration-implantation carcinoma, although theoretically possible, has not been proved Contiguity invasion and propagation directly through the bronchial lumen are important in all the histological types. Hilar tumors of squamous and adenomatous nature tend to extend centrifugally, those of undifferentiated type tend to extend centripetally and to mimic mediastinal lymphosarcoma The midzonal tumors tend to produce one of three pictures—an expanding mass, extension to the periphery, or metastasis to the hilar lymph nodes The governing factor in the two last-mentioned incidents probably lies in the portion of the lymphatic system involved and the direction of lymphatic flow The peripheral tumors tend to extend centrifugally mainly by contiguity invasion of adjacent tissues

The most frequent sites of metastases are the draining lymph nodes, bone, brain, liver, adrenals, kidneys, spleen, and heart. They may occur with limited or extensive lesions. The lymphatic route is the one favored by the undifferentiated tumors The peripheral group shows a greater tendency for extensive extrapulmonary contiguity invasion than any other group and may limit its spread to this route only, be free of intrathoracic metastases, and show only blood-borne metastases Nontumorous intrathoracic complications are common in the hilar group, are infectious in nature, and follow obstruction of the bronchial lumen

Surgical Pathology

The diagrams which follow are those of resected lungs that illustrate various features of bronchogenic carcinoma in its less extensive phases The site of origin is indicated by an arrow The dots illustrate the presence of tumor and its path of propagation

The findings are based on gross examination of the specimens and histological examination of serial blocks



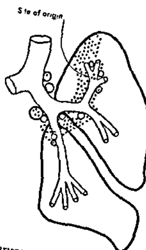
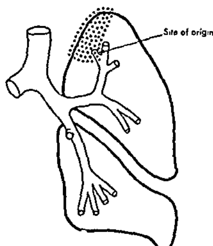


DIAGRAM I *Hilar Adenocarcinoma* The carcinoma arises in the anterior seg-
nental bronchus of the left upper lobe The routes of propagation are contiguity
nvasion and metastases to the hilar lymph nodes Lymphatic metastases are em-
obe in nature The lymphatic channels between the site of origin and the lymph
odes are free of tumor

IAGRAM II *Hilar Squamous Cell Carcinoma* The site of origin is the postero-
ical segmental bronchus of the left upper lobe The tumor shows lymphatic
rmeation peripherally to the pleura, centrally to the hilum, and distally to the
er lobe



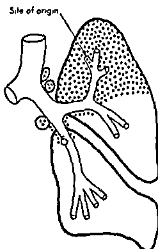
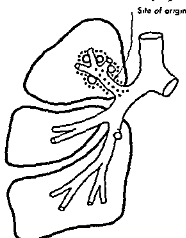


DIAGRAM III *Hilar Squamous Cell Carcinoma* The site of origin is the apical segmental bronchus of the left upper lobe The tumor extends peripherally, destroying all normal elements, penetrates through the pleura, and by contiguity invasion extends into the extrapulmonary tissues around the apex. The hilar lymph nodes are free of metastases

DIAGRAM IV *Hilar Squamous Cell Carcinoma* The site of origin is the apical segmental bronchus of the left upper lobe There is extensive lymphatic permeation through the upper half of the lobe and along the lobar bronchus into the apex of the lower lobe The hilar lymph nodes have metastases.



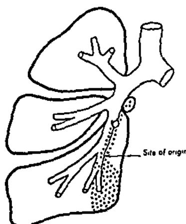
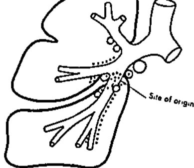


DIAGRAM V *Hilar Squamous Cell Carcinoma* The site of origin is the right upper lobar bronchus Locally, there is contiguity invasion and lymphatic permeation Veins are compressed but not invaded No hilar lymphatic metastases

DIAGRAM VI *Hilar Squamous Cell Carcinoma* The site of origin is the antero-medial basal bronchus of the right lower lobe. There is extensive contiguity invasion with necrosis, producing cavitation The tumor extends along the surface to the mouth of the superior (apical) bronchus The lymphatic permeation, distally, extends to the pleura, and proximally, through the peribronchial channels to the hilar lymph nodes



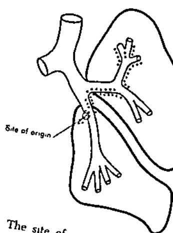
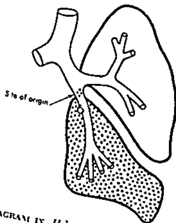


DIAGRAM VII *Hilar Squamous Cell Carcinoma* The site of origin is the right lower lobar bronchus There is local contiguity invasion and lymphatic permeation distally and up into the upper lobe One hilar lymph node has metastases

DIAGRAM VIII *Hilar Squamous Cell Carcinoma* The site of origin is the superior (apical) bronchus There is local contiguity invasion and surface extension up into the upper lobar bronchus There is also peribronchial lymphatic permeation into the upper lobe and penetration into the lumen of the postero-apical bronchus Hilar lymphatic metastases are absent



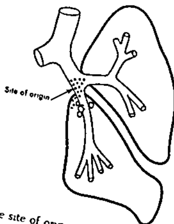
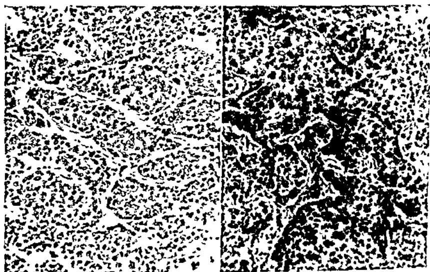


DIAGRAM IX *Hilar Squamous Cell Carcinoma* The site of origin is the left lower lobar bronchus An extremely extensive lymphatic permeation of the entire lower lobe produces a picture simulating a lobar pneumonia Near the site of origin there is local venous tumor thrombosis

DIAGRAM X *Hilar Squamous Cell Carcinoma* The site of origin is the medial wall of the left lower lobar bronchus A papillomatous mass projects into the lumen There is local invasion at the base of the tumor and surface extension at the edge

Experimental Pathology

Studies on heterologous transplantation of human lung cancer have revealed significant data which can be correlated with the clinical behavior of the disease. Greene transferred lung cancer to the eye and brain of experimental animals and found the tumor capable of autonomous growth in all instances. The tissue was obtained directly from the operating room



Heterologous Transplantation of Human Lung Cancer.

Fig 16 Epidermoid Carcinoma of Lung (surgical specimen).

Fig 17 Transplant of tumor in anterior chamber of guinea pig's eye.

(Courtesy of Dr Harry S N Greene *Cancer Research* 13.347 1953)

from either the primary lesion in the lung or a metastasis. The transplants were morphologically similar to the tumor used for transfer, and were not influenced in behavior by either histological type or derivation of the tissue

The uniformity of transplantability of lung cancer contrasted sharply with the results obtained in other malignancies In the routine heterologous transfer of unselected human tumors, only about half were capable of independent growth at the time of operation Greene found a consistent variation with respect to several organs In the breast, the majority of cancers were in a dependent phase and not transplantable at the time of the first surgical approach.

Heterotransplantability occurs late in the development of a cancer and can be correlated with the ability of the tumor to metastasize. Transplanta-

tion followed by autonomous growth is therefore indicative of an advanced stage of the tumor Most of the patients in this series were dead within a few months after surgery and all were dead within nine months The poor prognosis suggested by transplantability was thereby confirmed by the clinical course

The uniformity of success in the transplantation of bronchogenic carcinoma may be caused by its rapid development from dependency to autonomy, or to the advanced stage of lung cancer at the time of its clinical recognition The latter concept is corroborated by observations that (1) the disease may exist for years without any clinical manifestations, and (2) there is a paucity of cases found without metastases at time of surgical exploration

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IV

Clinical Manifestations

Clinical Duration

There are no accurate figures available in regard to the clinical duration of illness in bronchogenic carcinoma This is understandable inasmuch as most of the data must be furnished by the patient, and individual sensitivity to symptoms varies greatly. Unless the disease begins with a dramatic manifestation such as hemoptysis, pneumonia, or a neurological complication, few patients are able to recall the onset Most of the reliable data on this subject is therefore obtained fortuitously on the basis of previous roentgen films or hospitalizations for apparently unrelated conditions

The wide variation in the duration of illness is due in many instances to the insidious onset of the disease It is difficult for patients to take cognizance of an unproductive cough or a pain in the chest which does not seriously interfere with their activities The apparent recovery from mild pulmonary symptoms because of remission or medication further tends to dissociate the early symptoms of the disease from the disabling later ones

The second factor responsible for the great differences among patients in the duration of illness is the nature of the pathological changes induced by the tumor When the symptoms are mainly the result of slow bronchial obstruction the clinical history may extend back for years In cases in which the metastatic symptoms are predominant, the entire duration of illness, clinically, may be less than one month There were 91 patients (43 per cent) in our series with a clinical history of less than 6 months and 130 (62 per cent) of less than one year Out of 443 cases reported by Buchberg from the Montefiore Hospital, there were only 70 (15 8 per cent) who lived more than two years after the onset of obvious symptoms

A great deal of blame has been placed on patients for neglecting the early symptoms of the disease Overholt estimated that the average patient waits three months before seeking medical advice and that another seven months is lost in medical observation The latter period can undoubtedly be shortened by intensive medical investigation and alertness However,

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terminal category Less than 5 per cent of our patients lived more than six months after hospitalization and less than 1 per cent lived more than a year

Classification of Symptoms

As a result of roentgen studies, sufficient evidence has accumulated to show that bronchogenic carcinoma may exist for months, or even years, without producing any symptoms The asymptomatic phase has been particularly noted in peripheral lesions, which are usually detected in the course of routine examinations or surveys Bronchial tumors have also been found accidentally upon necropsy examination in patients dying of other conditions Furthermore it is now recognized that the first symptoms of bronchogenic carcinoma may be entirely non-pulmonary and the result of a metastatic focus Peripheral nerve palsy and hemiplegia frequently precede the onset of pulmonary symptoms, and many patients have been operated for brain tumor which subsequently proved to be a lung metastasis

There is no symptom-complex that characterizes the early stages of lung cancer (Table 1) Even in far-advanced cases the symptoms may be bizarre

TABLE 1 *Symptoms of Bronchogenic Carcinoma*

(Based on Admission Complaints of 210 Necropsied Cases)

THORACIC		EXTRATHORACIC				GENERAL	
Cough	158	Back pain	36	Vomiting	6	Weight loss	124
Dyspnea	100	Shoulder pain	20	Hemiplegia	4	Fever	97
Chest pain	91	Hoarseness	19	Convulsions	4	Emaciation	75
Hemoptysis	71	Extremity pain	10	Blindness	4	Anorexia	66
Wheezing	15	Extreme weakness	9	Arm paralysis	3	Night sweats	27
				Paresthesia	3		
		Subcutaneous mass	8	Aphasia	2		
				Facial palsy	2		
		Epigastric pain	8	Vertigo	2		
		Neck pain	7	Herpes zoster	2		
		Jaundice	7	Drowsiness	2		
		Sciatic pain	7	Psychosis	2		
		Headache	7	Facial swelling	1		
		Dysphagia	6				

and confusing For this reason a simple enumeration of the symptoms frequently encountered is of little diagnostic importance. In order to obtain a broad concept of the significance of the symptoms, they must be correlated with the pathological changes produced by the disease This provides a rational basis for the sequence of events and permits evaluation in regard to prognosis and operability Corresponding to the pathological findings, three categories of symptoms are recognized Tumor, Infection, and Metastatic (Table 2).

this will not completely solve the problem of early diagnosis because of the lack of relationship between duration of symptoms and the extent of the disease The symptoms of bronchogenic carcinoma depend on the nature and extent of the pathological processes One patient may have obvious symptoms for years and present a localized tumor, and in another patient the first symptoms may be due to an extrathoracic invasion In the series reported by Lindskog and Bloomer the duration of symptoms was longer in the resectable cases than it was in the nonresectable ones.

The short duration of symptoms in most of the patients in no way reflects the actual duration of the disease. Many patients with bronchogenic carcinoma have been observed to live five or six years and even longer. Six of our patients lived more than seven years Overholt and Schmidt reported a case in which an abnormal density on the roentgen film was observed for nine years At operation there was found a resectable bronchogenic carcinoma. White reported a case of eleven years' duration who lived four years after palliative surgery.

Rigler studied the duration of illness on the basis of previous roentgen examinations and found that in 37 inoperable patients the average duration of symptoms was 12.7 months and that roentgen signs had preceded the onset of symptoms by 7.8 months In 13 operable patients, the average duration of disease as determined by roentgen signs was 36 4 months. There is no doubt that the roentgen examination is a far more accurate index to duration of illness than are the patient's symptoms Unfortunately, in many instances the correct interpretation of early roentgen films is made only in retrospect.

Incidental pathologic findings and radiographic studies indicate that the duration of illness in bronchogenic carcinoma is far greater than is usually considered. It is highly probable that even in patients whose clinical manifestations are of brief duration the disease process has existed for several years

Duration of Hospitalization. The data on duration of hospitalization in our 210 cases was of considerable interest More than one-fourth of the patients died within 10 days of admission and more than half within 30 days This indicated the far-advanced status of the disease on entering the hospital Inasmuch as both hospitals in the study were municipal institutions, there was no financial requirement as a barrier to earlier hospitalization. Gittens, in his study at the Harlem Hospital, found the average duration of life after admission to be 46 5 days Possibly some of the patients desired to remain at home as long as they could, but it is more likely that disabling symptoms had not developed until shortly before hospital admission The fact that death ensued within a short time after entry emphasizes again that patients with bronchogenic carcinoma may live for long periods of time until a complication or metastasis develops which brings them into the pre-

tologic features of the tumor Cases have been described in which the patient expectorated in excess of a quart of sputum daily.

Ulceration Erosion of the tumor into the bronchial wall produces bleeding by involvement of venous and capillary channels The hemoptysis may be prolonged, depending on the extent of the ulceration, but is not usually severe On rare occasions, hemoptysis may be a profuse and terminal symptom The blood is usually mixed with scant mucoid sputum As bleeding continues for several days the color of the blood becomes dark and gives rise to the 'prune juice sputum' which was formerly considered pathognomonic of lung cancer. This dark coloring, however has been observed with all types of pulmonary hemorrhage and is indicative only of the long duration of the bleeding Frankly purulent sputum that contains small amounts of blood is usually not due to bronchial ulceration, but occurs as a result of parenchymal destruction distal to the tumor

In many ways hemoptysis is a very fortunate symptom, for it is too dramatic to disregard While the patient may ignore a chronic cough for many months, he will quickly seek medical advice for bleeding Hemoptysis does not occur in the majority of cases, however In our series it was present in 71 cases (34 per cent) and was the initial symptom in 12 cases (6 per cent) Continuous pulmonary bleeding is not very common in bronchogenic carcinoma Unless the diagnosis of malignancy is unequivocal, other conditions should be suspected Gradual perforation of a mycotic aneurysm of the aorta or other large vessel may produce hemorrhage into the lung and subsequent daily hemoptysis for many weeks

Obstruction The tumor may invade the submucosa or grow inward and encroach upon the bronchial lumen It usually does both in varying degrees If the bronchus of origin is a large one, the effects of encroachment are considerably delayed. Inasmuch as the bronchi widen and elongate in inspiration, the obstruction to the passage of air is more noticeable on expiration. Tumors in the smaller bronchi may produce a greater degree of anatomic obstruction but, because of the smaller segment of lung involved, the effect is not striking

In so far as the patient is concerned, the obstruction in the air passages is first manifested by a wheeze This is heard on the side of the chest corresponding to the location of the tumor It is usually inconstant and may be heard in one particular position and not in others As the obstruction becomes more complete, the wheeze disappears For these reasons, this symptom is rarely volunteered by the patient and must be specifically elicited There were only 15 patients (7 per cent) in our series who described the presence of a wheeze and in only 1 case was it the initial symptom Woodman reported an incidence of less than 4 per cent It is possible that more careful history-taking will reveal the existence of a wheeze in a greater proportion of patients Complete bronchial occlusion produces atelec-

TABLE 2. *Correlation of Symptoms and Pathological Findings*

Group 1	*Tumor Symptoms*
	(a) Irritation
	(b) Ulceration
	(c) Obstruction
	(d) Necrosis
Group 2	*Infection Symptoms*
	(a) Upper respiratory
	(b) Recurrent pneumonitis
	(c) Lobar pneumonia
	(d) Bronchiectatic
	(e) Pleuro-pericardial
Group 3	*Metastatic Symptoms*
	(a) Pleuro-pulmonary
	(b) Lymph node
	(c) Central nervous system
	(d) Peripheral nerves
	(e) Visceral

GROUP 1. TUMOR SYMPTOMS

Although bronchogenic carcinoma may occur anywhere along the bronchial tree the vast majority of tumors are found in the main, lobar, and segmental bronchi. The presence of the tumor is manifested in four distinct ways. Irritation, Ulceration, Obstruction, and Necrosis. The symptoms produced by these pathological processes depend on the size of the tumor, the depth of the tumor in the bronchial wall, and the location of the tumor along the bronchial divisions

Irritation Bronchial tumors that arise in sensitive areas, such as the region of the major bronchi below the carina, act as foreign bodies and produce paroxysms of cough out of proportion to the size of the growth. The cough is fairly constant and either entirely unproductive or accompanied by the expectoration of scant mucoid sputum Tumors that are located in the lobar bronchi or their subdivisions may not produce cough for long periods of time. In these cases, the occurrence of cough is usually the result of distal parenchymal infection rather than of irritation Tumors that arise from small bronchi and bronchioli may attain considerable size without producing cough These are the silent peripheral lesions which are detected on routine X-ray films far in advance of clinical symptoms.

Most observers have commented on the frequency of cough as a symptom of bronchogenic carcinoma. In our series of 210 cases, cough was a prominent feature in 158 (75 per cent) In 53 of these cases (25 per cent) the fact that there was very little expectoration indicated that the cough was the result of irritation of the bronchial mucosa There were 59 patients (28 per cent) who stated that cough was the initial symptom of the disease.

Tumors arising from terminal bronchioles and extending into the alveolar spaces (alveolar cell tumors) have been associated with the expectoration of large amounts of frothy, mucoid sputum. This is due to the peculiar his-

SYNOPSIS Male, aged 54, was hospitalized in May 1946 complaining of cough and wheezing of two months' duration The X ray showed an enlargement of the left hilar shadow with linear radiations extending into the left upper lobe. Bronchoscopy was negative. Following the bronchoscopy the patient's symptoms improved and he was discharged in June 1946

One year later the patient again requested hospitalization The cough had recurred shortly after his previous discharge and had become progressively worse. He was also aware of dyspnea on exertion X ray in May 1947 showed the left upper lobe to be atelectatic with deviation of the mediastinum to the left Bronchoscopy was again negative. Exploratory thoracotomy was sug-



Case Illustration No 1. *Patient C J.* 17 *February* 1948

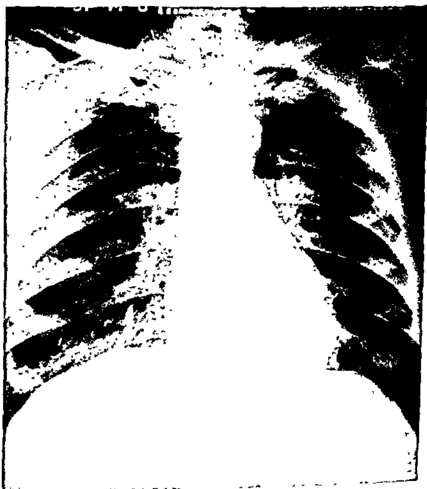
FIG 2 Growth *of the tumor in the intervening two years has resulted in* marked atelectasis of the entire left lung

tasis of the corresponding lung tissue. When the larger bronchi are involved, dyspnea may be a prominent symptom.

CASE ILLUSTRATION No 1, PATIENT C. J. (Figs 1 and 2)

DIAGNOSIS. Bronchogenic carcinoma, left upper lobe.

SIGNIFICANT FEATURES Serial X rays in the course of two years' observation depict the progressive pulmonary changes produced by bronchial obstruction Procrastination of therapy was due to the absence of positive findings in the early roentgen and bronchoscopic studies.



Case Illustration No 1. Patient C J *14 May 1946*

FIG 1 The left hilar shadow is increased in size and there are linear radiations extending into the left upper lobe.

SYNOPSIS Male, aged 54, was hospitalized in May 1946 complaining of cough and wheezing of two months' duration The X ray showed an enlargement of the left hilar shadow with linear radiations extending into the left upper lobe Bronchoscopy was negative Following the bronchoscopy the patient's symptoms improved and he was discharged in June 1946

One year later the patient again requested hospitalization The cough had recurred shortly after his previous discharge and had become progressively worse. He was also aware of dyspnea on exertion X ray in May 1947 showed the left upper lobe to be atelectatic with deviation of the mediastinum to the left Bronchoscopy was again negative Exploratory thoracotomy was sug-



Case Illustration No 1 Patient C J *17 February* 1948

FIG 2 Growth of the tumor in the intervening two years has resulted in marked atelectasis of the entire left lung

gested but was refused, chiefly because of the medical reassurances given on the previous admission

The third hospitalization was in February 1948 He had become more dyspneic and hoarse. There was further atelectasis of the left lung and paralysis of the left vocal cord. A course of deep X-ray therapy was given as a palliative measure but this made the patient feel worse.

In August 1948, the patient developed an effusion on the left side which necessitated aspiration for relief of dyspnea He was again hospitalized and examination disclosed evidence of diffuse metastases. Death occurred on 10 May 1949, three years after the first hospital work-up

NECROPSY Squamous carcinoma, left upper lobe bronchus with extension into parenchyma of left upper lobe Metastatic lesions were present in the left pleura, left ribs, left hilar nodes, and pericardium

Necrosis Bronchogenic carcinoma may be limited to the bronchus of origin or may extend into the corresponding lobe. In many instances the entire lobe is replaced by tumor tissue which shows central necrosis and softening At times, huge abscesses are present. The absorption of toxic products into the general circulation is responsible for many of the systemic symptoms such as low grade fever, anorexia, malaise, lassitude, and weight loss Superimposed bacterial infection of the carcinomatous abscess accentuates these manifestations

GROUP 2 INFECTION SYMPTOMS

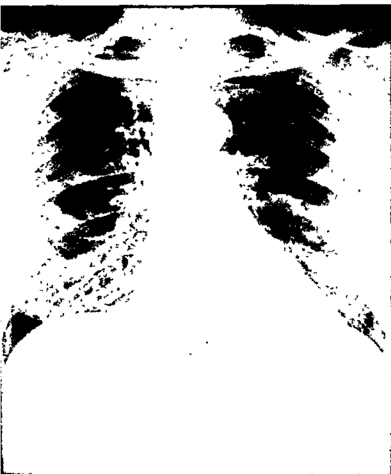
Bronchial obstruction, regardless of etiology, invariably results in some degree of infection in the adjacent lung tissue. In bronchogenic carcinoma, the persistence and progression of the obstruction make the secondary parenchymal infection an important source of symptoms It is not unusual for the earliest features of the illness to be due to the infectious process in the lung rather than to the tumor in the bronchus Various clinical syndromes are produced by the parenchymal infection which, unfortunately, are usually diagnosed in retrospect.

Upper Respiratory Syndrome The patient presents a history of repeated infections which appear to originate in the upper respiratory tract There is an acute onset of chilliness, low grade fever, malaise, and paroxysmal cough with mucoid expectoration The physical and roentgen examinations of the chest are negative. After a week or two the symptoms subside, only to recur in two or three weeks The clinical picture closely resembles recurrent pharyngeal, nasal, or sinus infection, and the correct diagnosis is usually delayed until the disease is far advanced Several months may elapse before there is any roentgen evidence of tumor.

CASE ILLUSTRATION No 2, PATIENT M P (Figs 3 and 4)

:NOSIS Bronchogenic carcinoma, left lower lobe.

IFICANT FEATURES Negative X rays, bronchoscopy, and bronchial secretions during four months of observation Diagnostic clues were (1) recurrent respiratory infections, (2) persistent subfebrile temperature, (3) increased sedimentation rate, and (4) eosinophilia



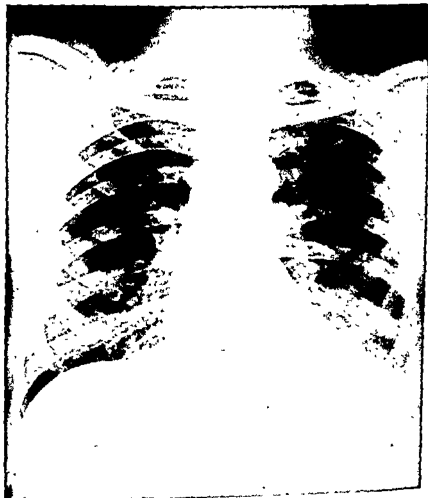
se Illustration No 2 Patient M P 24 *March* 1945

: 3 There is no evidence of a lesion in the left lower lobe and the left costo-renic sinus is clear Previous films in January and February 1945 were also gative

SYNOPSIS Male, aged 55, developed moderately severe respiratory infection in December 1944 This was followed by several similar episodes, each characterized by paroxysmal cough and fever. There was a weight loss of twelve pounds within three months.

X rays in December 1944 and March 1945 were negative. Physical examination of chest repeatedly negative. Bronchoscopy and examination of bronchial secretions negative in May 1945. Increased sedimentation rate and eosinophilia noted from March to May 1945

In May 1945 cough became continuous and examination on 14 May disclosed diminished breath sounds and dullness over the left lower lobe poste-



Case Illustration No 2 Patient M P *14 May 1945*

FIG. 4 Slight haziness at left base This was first significant X-ray finding after four months' observation

riorly X ray taken that day showed haziness at the left base The effusion increased very rapidly and in two weeks filled the entire left chest. The patient expired on 28 July 1945, about seven months after the onset of his symptoms

NECROPSY. Squamous cell carcinoma of tertiary bronchus, left lower lobe with metastases to left pleura, hilar nodes, and ribs.

There are certain features of this syndrome that serve as clues to the underlying process. (1) a negative history of previous respiratory disease, (2) weight loss out of proportion to duration and severity of symptoms, (3) subfebrile temperature in intervals between acute episodes, (4) fatigability, (5) dyspnea on slight exertion, and (6) persistently rapid erythrocyte sedimentation rate and leukocytosis Evidence of this type is non-specific and calls for much further investigation However, the upper respiratory syndrome may precede the onset of definite pulmonary symptoms for three or four months and possibly longer.

Recurrent Pneumonitis Syndrome. The history, physical signs, and X-ray studies are all compatible with the diagnosis of bronchopneumonia. At the first observation, no other diagnosis is usually tenable. It is only after the episode has been repeated within a short period of time that suspicion is directed toward the presence of an endobronchial lesion. The X ray shows involvement of the same adjacent pulmonary segments each time It is to be emphasized that the patient may not be acutely ill and that resolution of the pneumonic infiltration may be complete with each episode An apparently successful therapeutic response to antibiotic drugs is often misleading regarding the true nature of the underlying process

CASE ILLUSTRATION NO. 3, PATIENT R R (Figs 5 and 6)

DIAGNOSIS Bronchogenic carcinoma, left lower lobe

SIGNIFICANT FEATURES Negative X rays, negative bronchoscopy and bronchial secretions during two months of observation Diagnostic clues were (1) recurrent episodes of pneumonitis, (2) persistent fever, (3) increased sedimentation rate, (4) eosinophilia, and (5) leukocytosis.

SYNOPSIS. Male, aged 59, with history of dry cough of ten years' duration During the first week of January 1947 he was treated for pneumonia, following which he observed a persistent afternoon rise in temperature Physical examination on 11 February 1947 was essentially negative. X ray showed an old tuberculosis lesion at the right apex and right hilar calcification The left lung was clear Bronchoscopy was negative as was a Papanicolaou stain of the bronchial secretions. The sedimentation rate was 28 mm per hour The fever subsided following bronchoscopy and penicillin therapy

On 12 March 1947 the patient had another episode of pneumonia which was localized by physical examination and X ray to the left lower lobe The sedimentation rate was 44 mm per hour and the blood count showed 22,000 W.B C with 65 per cent polymorphonuclear neutrophiles and 6 per cent eosinophiles There was no anemia Bronchoscopy on 26 March 1947 was

again negative, but pathological examination of the bronchial secretions showed squamous carcinoma.

Pneumonectomy on 3 April 1947 revealed a small tumor in the left lower lobe straddling the posterior and lateral basal tertiary bronchi Distal to the tumor were small bronchiectatic abscesses. The patient died on 12 April 1947 as a result of sudden hemorrhage due to fracture of a rib.

NECROPSY. Squamous cell carcinoma limited to the left lower lobe bronchi, no metastatic lesions Incidental findings were fibrocavernous tuberculosis of right apex and healed miliary tuberculosis of the liver.

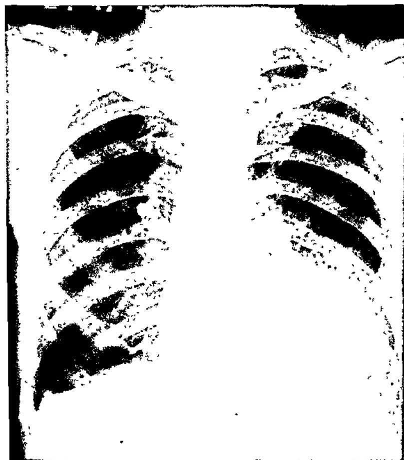
Lobar Pneumonia Syndrome. The clinical onset of bronchogenic carcinoma may be ushered in by symptoms duplicating those of lobar pneumonia.



Case Illustration No 3 Patient R R. *12 February 1947*

Fig 5 The thorax is emphysematous At the right apex there is an infiltration suggestive of an old tuberculous process. The right hilar glands show marked calcification The left lung is negative

This occurs when the tumor is situated near the orifice of a lobar bronchus The absence of previous pulmonary symptoms and the history of acute onset of chills, fever, chest pain, and the other familiar aspects of lobar pneumonia provide scant basis to consider an underlying malignancy It is only when the X ray shows little tendency of the lesion to resolve that suspicion of endobronchial diseases is excited Necropsy examination has not infrequently changed a clinical diagnosis of lobar pneumonia complicated by cirrhosis to bronchogenic carcinoma with hepatic metastasis. Cases with a



Case Illustration No 3 Patient R R *24 March 1947*

Fig 6 The appearance of the right lung is identical with that of the previous film On the left side there is a pneumonic consolidation limited to the left lower lobe

pneumonic onset are very often treated as lobar pneumonia for prolonged periods.

Case Illustration No 4, Patient K. K (Figs. 7 and 8)

DIAGNOSIS Bronchogenic carcinoma, right upper lobe

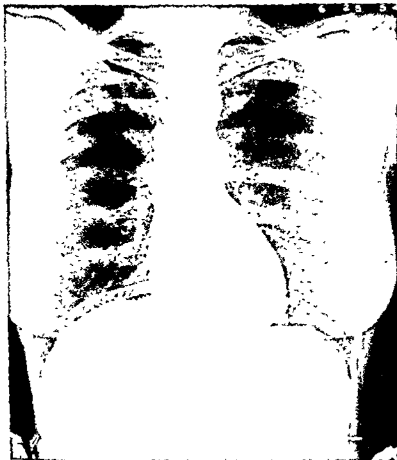
SIGNIFICANT FEATURES. Equivocal roentgen findings, negative cytological studies of sputum and bronchial secretions, negative bronchoscopy, diagnosis suspected because of persistence of small infiltrate after acute pneumonic symptoms had subsided.



Case Illustration No. 4 Patient K K.

Fig 7 There is a large round density in the right upper lobe below the clavicle; the right lower lobe shows pneumonic consolidation. The left lung is negative.

SYNOPSIS. Female, aged 63, with history of pneumonia in September 1953. Acute phase lasted one week but cough persisted In March 1954 became acutely ill again and X ray showed a round infiltration in the right upper lobe and consolidation in the right lower lobe (Fig. 7). Sputum negative for tubercle bacilli and malignancy. On antibiotic therapy the pneumonic lesion in the right lower lobe cleared up completely and the round lesion in the upper lobe decreased considerably in size The patient was asymptomatic for the succeeding five months, during which time serial X rays showed persistence of the small infiltration in the right upper lobe (see Fig 8)



Case Illustration No 4 Patient K K

Fig 8 Comparative film three months later shows the density in the right upper lobe to have diminished in size considerably There is no evidence of the pneumonic consolidation in the lower lobe previously noted

Exploratory thoracotomy on 13 August 1954 showed a tumor mass in the right upper lobe with metastatic involvement of the adjacent hilar lymph nodes Right pneumonectomy was performed

SURGICAL PATHOLOGY Bronchiologenic carcinoma arising from the broncho-pulmonary segment of the right upper lobe. The tumor mass measured 2 x 1 cm and was fairly well circumscribed Metastases were present in the hilar lymph nodes adjacent to the middle lobe. The carinal and paratracheal nodes were negative The middle and lower lobes showed no evidence of malignancy An incidental finding was the presence of nests of fibrotic and caseous tubercles throughout the entire right lung. Microscopy showed the alveoli lined by malignant cells with the normal alveolar pattern preserved

Bronchiectatic Syndrome. The frequent occurrence of pulmonary infection distal to the bronchial tumor produces bronchiectatic abscesses in a considerable number of cases. These bronchiectatic changes often dominate the clinical scene and are to be differentiated from abscesses that result from the necrosis of tumor tissue In our series there were 70 cases (33 per cent) with bronchiectatic abscesses, some of which had attained a fairly large size As in all bronchiectasis, the essential feature is the extent of the pulmonary infection rather than the size of the ectatic bronchus Large abscesses, however, are indicative of widespread broncho-pulmonary necrosis

The outstanding symptoms of bronchiectatic disease are cough and expectoration These symptoms occur with great frequency in bronchogenic carcinoma and are due in the majority of instances to the bronchiectatic changes distal to the tumor rather than to the carcinoma itself The sputum is purulent and not infrequently foul Copious amounts may be expectorated, especially in the morning The fact that the patient gives a history of productive cough of long duration does not exclude the possibility that malignancy may be responsible for the bronchiectasis Although frank hemoptysis may occur as a result of ectasia, it is more common to find blood-streaked expectoration

Bronchiectasis may also occur in regions of the lung remotely situated *from the site of the tumor Necropsy has not infrequently shown* bilateral lower lobe ectasia associated with upper lobe tumor. This was found in more than 10 per cent of our cases. There is a possibility that bronchiectasis of this type antedated the occurrence of the carcinoma There are, however, frequent opportunities for *bronchogenic spread of infectious material* to the lower lobes. The existence of lower lobe bronchiectasis does not, therefore, always indicate extension downward of the tumor with subsequent infection.

Pleuro-Pericardial Syndrome The occurrence of pleural or pericardial effusion in patients with bronchogenic carcinoma is usually regarded as evidence of metastatic invasion of these serous membranes While this assumption may be correct in many instances, it should also be recognized that pleurisy and pericarditis may result from infection secondary to the

tumor This is a very important consideration in discussions of operability In our series there were 47 cases (22 per cent) of pleural effusion without neoplastic invasion of the pleura There were also 15 cases (7 per cent) of empyema Pericarditis and pericardial effusion occurred in 27 cases (13 per cent).

CASE ILLUSTRATION No 5, PATIENT H E (Fig 9)

DIAGNOSIS Bronchogenic carcinoma, right upper lobe

SIGNIFICANT FEATURES The entire pulmonary history prior to hospitalization was of three weeks' duration Necropsy examination showed that the symptoms which brought the patient under observation were not due to the tumor itself but were the result of secondary inflammatory changes in the lung and pleura

SYNOPSIS Male, aged 66, was hospitalized on 16 October 1948 complaining of cough, pain in the right side, shortness of breath, and fever of three weeks duration X-ray examination disclosed a homogeneous density in the lower two thirds of the right chest This was interpreted as fluid, probably the result of metastatic involvement of the pleura An X ray taken three weeks later showed apparent increase of the fluid to the right apex Diagnostic thoracentesis was repeatedly unsuccessful The clinical course was progressive and the patient died on 18 November 1948 three days after the last X ray

NECROPSY Anaplastic carcinoma of the right upper lobe bronchus extending down into the middle and lower lobe bronchi Distal to the tumor in the lower lobe was a large abscess Metastatic lesions were present in the pericardium and in the tracheobronchial, mediastinal, and abdominal lymph nodes

There was a diffuse fibrinous pleurisy involving the entire right hemi-thorax but no free fluid There was no evidence of metastatic extension to the pleura

IMPORTANCE OF INFECTION

The majority of pulmonary symptoms associated with bronchogenic carcinoma are not due primarily to the tumor but are the result of infection distal to the tumor Unproductive cough, hemoptysis, and wheezing may be due solely to the bronchial growth, but purulent expectoration, fever, night sweats, anorexia, malaise, weakness, and weight loss are the manifestations of parenchymal infection Cough and hemoptysis, two of the cardinal symptoms of the disease, are more often the result of secondary bronchiectatic changes than of the carcinoma itself The toxic systemic symptoms are closely related to the extent and severity of the inflammatory changes This explains the differences in physical deterioration among the patients despite the unity of the primary diagnosis

The syndromes of atypical upper respiratory infection, recurrent pneumonitis, and lobar pneumonia are all due to the infection and not to the carcinoma per se An understanding of the infectious processes in the lung is therefore paramount in the appreciation and evaluation of the symptoms of bronchogenic tumor The interest in viral infections of the lung during the past decade has led to many delays in the diagnosis of bronchogenic carcinoma Prolonged resolution of pulmonary lesions in an asymptomatic

illness The extensive metastases found on necropsy contrasted greatly with the brief duration of the pulmonary symptoms.

SYNOPSIS Female, age 70, was hospitalized on 7 August 1945 complaining of a fifteen-pound weight loss during the previous year. Six weeks before admission she had become short of breath and during the week preceding hospitalization she had had several hemoptyses The admission X ray showed diffuse nodular dissemination throughout both lung fields and metastatic destructive areas in several of the ribs The liver was enlarged and nodular The clinical picture was that of generalized carcinomatosis in a terminal stage.

NECROPSY Adenocarcinoma of the left upper lobe with generalized dissemination Both lungs and pleura were studded with pearly hard masses There were bilateral pleural effusions. Metastatic lesions were present in the liver and in the left seventh, eighth, ninth, and tenth ribs.

GROUP 3 METASTATIC SYMPTOMS

The tendency for bronchogenic carcinoma to metastasize early, frequently, and profusely has been well established. There is, however, a wide discrepancy between the number of metastases recognized clinically and those found on necropsy examination. The ability of many patients to bear with their metastatic lesions for prolonged periods, even years, has often given rise to the clinical illusion that bronchogenic carcinoma is a localized disease That this is far from the truth is attested by the large number of patients subjected to surgery and found inoperable on exploratory thoracotomy (Chapter I—Table 1) The number of patients who succumb to

TABLE 3 *Initial Symptoms Due to Metastases (89 Cases)*

			CASES
I	*Pain*		52
	Thoracic	24	
	Shoulder	9	
	Back	8	
	Epigastric	4	
	Sciatic	3	
	Arm	2	
	Hip	1	
	Neck	1	
2	*Dyspnea*		13
3	*Extremity weakness*		7
4	*Cerebral*		7
	Headache and vertigo	4	
	Drowsiness	2	
	Hemiparesis	1	
5	*Subcutaneous mass*		4
	Neck	2	
	Chest	1	
	Groin	1	
6	*Hoarseness*		4
7.	*Facial edema*		1
8	*Vomiting*		1

the disease without metastases is very small In our series of 210 cases there were but 7 (3 per cent)

Pathological studies have shown that there is scarcely an organ of the body that is immune to metastatic invasion from bronchogenic carcinoma The lymph nodes, particularly the tracheobronchial and the mediastinal, showed the greatest number of lesions The liver, bones, pleura, adrenal, cardiovascular system, contralateral lung, brain, and kidney also showed a high degree of involvement Less frequently implicated were the gastrointestinal tract, spleen, pancreas, skin, and subcutaneous tissue and muscles The thyroid and ovary were involved rarely.

Early Metastatic Symptoms The importance of metastatic foci becomes evident when it is realized that in a large number of patients the first clinical manifestation of bronchogenic carcinoma is due to a metastasis (Table 3) There were 89 patients (42 per cent) in our series in whom the initial symptom of the disease was apparently the result of metastatic invasion Paulson and Shaw found that in 25 per cent of 362 patients the initial complaint precluded operability The outstanding early metastatic symptom was pain which occurred in 52 cases Dyspnea, extremity weakness, and cerebral symptoms were next in frequency

Case Illustration No 7, Patient J H (Fig. 11)

DIAGNOSIS Bronchogenic carcinoma, right upper lobe

SIGNIFICANT FEATURES Neurological symptoms due to metastases dominated the entire course of illness There were no pulmonary complaints at any time Serial chest films during two months of observation showed minimal fibrosis in the right upper lobe The diagnostic clue was the presence of multiple osseous metastatic foci X-ray evidence of an expanding pulmonary lesion occurred very late in the disease.

SYNOPSIS Male, aged 45, was hospitalized on 25 December 1947 for right scapular pain of two months' duration and low back pain of two weeks' duration X-ray examination disclosed minimal fibrosis at the right apex and destructive changes in several of the dorsal vertebrae The blood count showed a moderate leukocytosis and the sedimentation rate was elevated

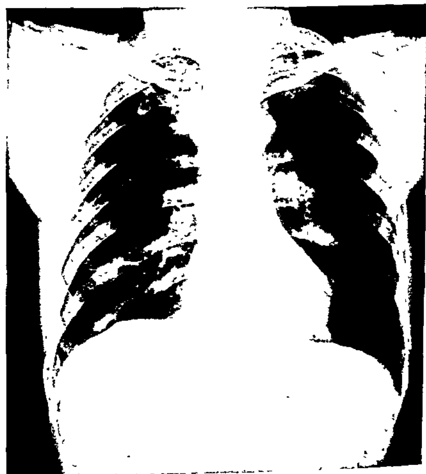
The scapular and lumbar pains increased in severity and within two weeks of admission there was a frank paraplegia The clinical course was characterized by progressive anemia and weight loss An X ray taken two months after admission showed a definite lesion in the right upper lobe for the first time Death occurred on 3 March 1948

NECROPSY Squamous carcinoma, originating distal to the tertiary divisions of the right upper lobe bronchi The right apex was comprised of solid tumor tissue Malignant thromboses were present in the pulmonary, hepatic, and portal veins and malignant emboli in the pulmonary arteries

There was diffuse metastatic lymph node invasion involving the tracheobronchial, pancreatic, peri-aortic, and mesenteric glands The left pleura was involved by way of lymphatic permeation across the vertebrae Metastatic

destructive lesions were present in the following dorsal vertebrae: first, third, fourth, fifth, ninth, and tenth.

Thoracic pain does not always imply metastatic invasion and may be due to inflammatory changes in the pleura associated with parenchymal infection. However, thoracic pain that is persistent and progressive is usually due to malignancy. Pain in the spine and extremities is usually the result of vertebral destruction. In one-fourth of the patients in the series pain was the first symptom of bronchogenic carcinoma, and in one-eighth the pain was extrathoracic. The difficulty in diagnosing cases in the latter group requires no elaboration. The temporary response of the pain to physical therapy, and



Case Illustration No. 7. Patient J H

Fig 11 There is minimal fibrosis at the right apex The remainder of the parenchyma is negative (Metastatic symptoms present at this time)

the occasional spontaneous remissions, added further to the delay in the recognition of the primary disease

When dyspnea occurs as the initial symptom it is usually the result of pleural invasion and effusion It may occur in the course of the disease as a consequence of mediastinal compression by enlarged nodes Dyspnea is also produced by bronchial obstruction caused by the tumor itself In seven of our patients, the first symptom was due to metastasis to the brain. One of these patients was operated for brain tumor because of the absence of definite roentgen findings in the chest There were four patients whose initial complaint was that of a subcutaneous mass, in one instance the mass was located in the groin Hoarseness was the first symptom in four cases and was due to involvement of the recurrent laryngeal nerve In one patient the initial complaint was facial edema, which was a result of compression of the superior vena cava by enlarged nodes

Case Illustration No 8, Patient R L P (Fig 12)

DIAGNOSIS Bronchogenic carcinoma, left upper lobe

SIGNIFICANT FEATURES The first clinical manifestation of the tumor was hydrothorax which resulted from metastatic involvement of the pleura There were no premonitory phases

SYNOPSIS Male, aged 43, developed an upper respiratory infection in October 1947 The acute symptoms subsided after three days, but the patient was aware of exertional dyspnea when he tried to resume work Two days later he consulted a physician, who found a massive pleural effusion on the left side

Repeated aspirations were required during the succeeding two months for relief of dyspnea, and the patient was subsequently hospitalized on 30 December 1947 The blood count showed a leukocytosis of 18,000 and the sedimentation rate was elevated The pleural fluid was negative for tubercle bacilli and malignant cells The clinical course was characterized by progressive accumulation of pleural fluid and pain in the left hemi-thorax Death occurred on 1 April 1948

NECROPSY Adenocarcinoma, lingular branch of left upper lobe bronchus, with direct extension to pleura, diaphragm, and intercostal tissues Metastatic lesions were present in the tracheobronchial, aortic, and upper abdominal lymph nodes

The fact that the first symptom of bronchogenic carcinoma may be due to a metastatic focus implies that there exists a silent, or latent, stage which antedates the invasive manifestations In the present state of our knowledge this latent stage can be detected only by the routine roentgen film, although even this may fail on occasion Cases have been observed in which the X ray of the lungs was apparently negative while that of the spine showed obvious metastases, and the correct diagnosis was established only at necropsy It is possible that more careful history-taking will reveal in the future a

larger proportion of patients whose first symptom is due to the tumor and not of its metastases. A greater awareness of the various atypical syndromes previously described will help in this direction

CORRELATION OF SYMPTOMS AND METASTASES

Bronchogenic carcinoma may metastasize early or late in the course of the disease. In some instances anatomic considerations, such as proximity to



Case Illustration No 8 Patient R L. P

FIG 12. Massive left pleural effusion (metastatic) as first evidence of lingular adenocarcinoma Hydropneumothorax is the result of repeated aspirations to relieve dyspnea.

lymphatic structures, offer explanation for rapid invasion. In other cases hematogenous spread to a distant organ (adrenal or kidney) may occur early for no apparent reason If the patient survives any length of time many metastatic lesions eventually develop, some of which can be detected clinically Not infrequently the symptoms of a metastasis may completely dominate the clinical picture, as occurs with cerebral involvement The large variety of metastatic symptoms (Table 1) offers a striking contrast to the relatively few symptoms produced by the bronchial tumor Correlation of the metastatic lesions with their symptoms provides explanation for many of the atypical syndromes observed clinically

Pleuro-Pulmonary Metastatic involvement of the pleura not infrequently causes the first clinical manifestations of bronchogenic carcinoma Tumors arising from the terminal bronchioles are usually asymptomatic until the pleura is invaded Pain and dyspnea may be very marked from the onset Pleural metastases may also occur late in the disease. The development of pleural effusion may be very rapid, producing severe respiratory embarrassment within a few days Metastatic spread to adjacent lobes may produce few additional symptoms, but widespread lymphatic extension or dissemination from multicentric tumors is usually associated with marked dyspnea and weakness

Lymph Nodes Few cases escape involvement of the tracheobronchial nodes but in most instances the enlargement is not sufficient to produce compression symptoms, such as pain and dyspnea On occasion, even massive adenopathy produces relatively little discomfort However, retrosternal pain and dyspnea may be caused by tracheobronchial adenopathy, especially when combined with enlargement of the mediastinal glands Swelling of the head may result from glandular pressure on the superior vena cava

Metastases to the cervical, axillary and inguinal lymph nodes produce subcutaneous masses which occasionally break down to form draining sinuses These suppurative masses often resemble primary lesions and cause considerable confusion in diagnosis Involvement of the upper abdominal lymph nodes, particularly the peri-pancreatic, produces a syndrome indistinguishable from biliary or pancreatic malignancy Epigastric pain and jaundice are the prominent symptoms

CASE ILLUSTRATION NO 9, PATIENT A A H (Fig 13)

DIAGNOSIS Bronchogenic carcinoma, right upper lobe

SIGNIFICANT FEATURES The clinical manifestations were those of abdominal neoplasm with obstructive jaundice The pulmonary lesion was diagnosed as right upper lobe pneumonia and was considered as an incidental occurrence

SYNOPSIS Male aged 57, was hospitalized on 4 February 1949 with a history of abdominal pain jaundice and fever of two months duration The liver was markedly enlarged and tender The skin and sclerae were icteric and the stools were clay-colored The alkaline phosphatase was 25 B U The cephalin floc

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Pleuro-Pulmonary Metastatic involvement of the pleura not infrequently causes the first clinical manifestations of bronchogenic carcinoma Tumors arising from the terminal bronchioles are usually asymptomatic until the pleura is invaded Pain and dyspnea may be very marked from the onset. Pleural metastases may also occur late in the disease The development of pleural effusion may be very rapid, producing severe respiratory embarrassment within a few days Metastatic spread to adjacent lobes may produce few additional symptoms, but widespread lymphatic extension or dissemination from multicentric tumors is usually associated with marked dyspnea and weakness

Lymph Nodes Few cases escape involvement of the tracheobronchial nodes but in most instances the enlargement is not sufficient to produce compression symptoms, such as pain and dyspnea On occasion, even massive adenopathy produces relatively little discomfort However, retrosternal pain and dyspnea may be caused by tracheobronchial adenopathy, especially when combined with enlargement of the mediastinal glands. Swelling of the head may result from glandular pressure on the superior vena cava.

Metastases to the cervical, axillary, and inguinal lymph nodes produce subcutaneous masses which occasionally break down to form draining sinuses These suppurative masses often resemble primary lesions and cause considerable confusion in diagnosis Involvement of the upper abdominal lymph nodes, particularly the peri-pancreatic, produces a syndrome indistinguishable from biliary or pancreatic malignancy. Epigastric pain and jaundice are the prominent symptoms

Case Illustration No 9, Patient A A H (Fig. 13)

DIAGNOSIS *Bronchogenic carcinoma, right upper lobe.*

SIGNIFICANT FEATURES The clinical manifestations were those of abdominal [illegible]

SYNO[illegible]

abdominal pain, jaundice, and fever of two months duration. The liver was markedly enlarged and tender The skin and sclerae were icteric, and the stools were clay-colored The alkaline phosphatase was 25 B U The cephalin floc-

culation test was one plus, the thymol turbidity test was *six units, and the* cholesterol-ester ratio was 181/58 The urine was bile-stained

Physical examination of the thorax on admission revealed dullness over the right upper lobe and crepitant rales at both bases The X ray showed consolidation of the right upper lobe and a density below the fissure adjacent to the hilum Subsequent films showed partial clearing of both shadows The course of illness was progressive, with manifestations of cholemia and uremia Death occurred on 7 March 1949



Case Illustration No 9 Patient A A H

FIG 13 There is a homogeneous consolidation of the lower half of the right upper lobe Below the fissure and adjacent to the hilum is a dense circumscribed area with peripheral radiations The right diaphragm is elevated (Jaundice and abdominal pain were the predominant symptoms.)

NECROPSY Anaplastic carcinoma of right upper lobe bronchus with lymphatic permeation to pleura The tracheobronchial, cervical, and upper abdominal lymph nodes showed metastatic involvement Extensive malignant lesions were present in the liver, spleen, and pancreas

Central Nervous System The most significant metastatic symptoms are due to involvement of the nervous system, central and peripheral The number and variety of symptoms attributable to neurological involvement indicate a higher percentage of metastases than was found in the necropsy studies This may be explained by the inability to secure permission to examine the brain and spinal cord in all cases and the failure to note all peripheral nerve lesions The symptoms produced by cerebral involvement are compatible with the diagnosis of primary brain tumor Headaches, vertigo, Jacksonian convulsions, hemiplegia, blindness, vomiting, aphasia, drowsiness, and psychoses have all been observed at various times Diabetes insipidus due to posterior pituitary metastasis has been reported An X ray of the chest is therefore an indispensable part of the diagnostic work-up of every case of suspected brain tumor

Peripheral Nerves Metastatic foci in the vertebrae and spinal nerves are responsible for many of the syndromes encountered. Pain in the neck, back, and extremities is often the first and most prominent feature of pulmonary carcinoma Patients are often diagnosed as cases of peripheral neuritis or bursitis with little thought to the possibility of a primary disease Herpes zoster has also been observed on occasion Hiccough may be of central origin or may arise from direct invasion of the phrenic nerve Pain in the shoulder radiating down the arm to the fingers is due to destruction of the brachial plexus This syndrome, particularly when associated with chest pain, resembles the clinical picture in coronary artery disease Muscular weakness, paralysis, and atrophy of the upper extremity also occur in a significant number of instances Hoarseness may be due to direct invasion of the recurrent laryngeal nerve

Abdominal Viscera Although invasion of the liver, adrenal, and kidney is common in bronchogenic carcinoma, characteristic symptoms are rarely observed On occasion, pain in the loin and hematuria are noted in adrenal and kidney lesions Addison's disease as a result of metastatic bronchogenic carcinoma is exceedingly rare but has been reported Metastatic lesions are found in the gastro-intestinal tract not infrequently, and are for the most part asymptomatic Esophageal invasion produces dysphagia

Cardiovascular metastases occur in a significant number of instances and may produce disturbances in rhythm, congestive failure due to hemopericardium, and thrombo-embolic phenomena of the heart and pulmonary vessels Fisher, Hochberg, and Wilensky called attention to recurrent peripheral thrombophlebitis as a clue to carcinoma of the lung as well as to visceral cancer Right heart failure due to lymphangitic carcinomatosis and direct extension of the tumor has also been observed

Apical Tumors

The metastatic symptoms that have aroused the most interest are those produced by tumors at the apex of the lung In 1932, Pancoast described a syndrome characteristic of a special type of malignancy which he called the 'superior pulmonary sulcus tumor.' Subsequent studies have shown that the symptoms are based chiefly on anatomic considerations rather than on etiologic ones Peripheral bronchogenic malignancies located at the apices of the lung are most frequently associated with this syndrome, but it has also been observed in extrapulmonary tumors in the region of the lung apex.

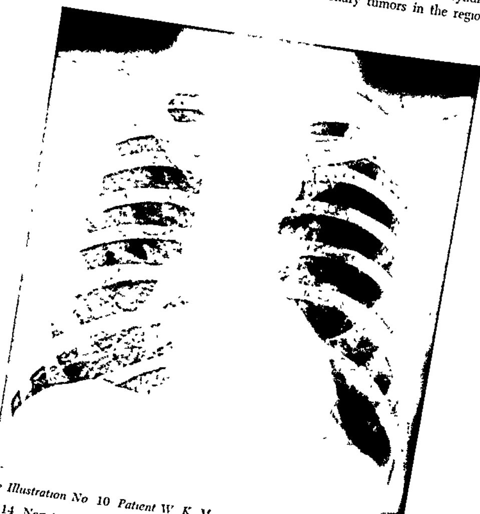
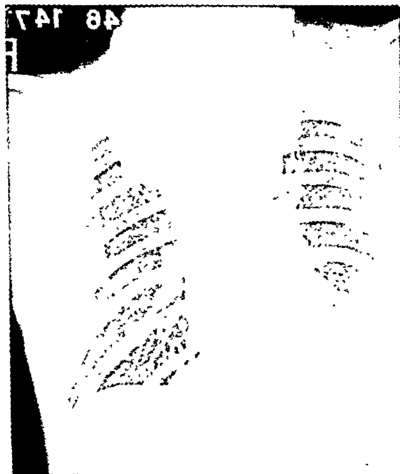


Illustration No 10 Patient W K M

14 Negative chest film (Symptoms suspicious of apical tumor) 2 May 1945

The symptoms of apical bronchogenic carcinoma are produced by metastases to the upper dorsal vertebrae, the upper ribs, the cervical sympathetic ganglia, and the brachial plexus The chief complaint is pain, which may be present in the upper chest, the shoulder, and the arm Not infrequently the pain radiates down the arm to the fingers Associated with the pain is progressive weakness of the corresponding upper extremity Paresthesia is also a frequent symptom The most dramatic feature of the tumor is the



Case Illustration No 10 Patient W K M *30 April 1946*

Fig 15 There is now a dense rounded mass in the right upper lobe extending down from the apex At the left base, above the diaphragm, is a homogeneous density suggesting pleural exudate

appearance of a Horner's syndrome. Pulmonary and systemic symptoms occur late in the course of the disease.

Case Illustration No 10, Patient W. K. M. (Figs. 14 and 15)

DIAGNOSIS Bronchogenic carcinoma, right upper lobe.

SIGNIFICANT FEATURES *This history illustrates the importance of repeated diagnostic studies in problem cases The symptoms suggested an apical tumor but the initial X ray was negative. Comparative films were not taken until eleven months later, at which time the tumor was obvious, roentgenologically as well as clinically.*

SYNOPSIS. Male, aged 49, complained of persistent right shoulder pain and right upper chest pain in May 1945. The chest film was negative Treatment consisted of physical therapy, which gave some relief. In February 1946 the patient noted a dry cough which gradually became productive and blood-tinged In the succeeding two months he lost thirty pounds

The patient was hospitalized on 6 April 1946. X-ray examination disclosed a mass in the right upper lobe extending down from the apex and an effusion at the left base Bronchoscopy was impossible because of tracheal compression. Laryngoscopy revealed edema of the larynx and partial paralysis of the right vocal cord The clinical course was characterized by fever, tachycardia, and inanition. Death occurred on 5 May 1946.

NECROPSY Squamous carcinoma of the right apex with no apparent bronchial origin The trachea and esophagus were invaded and distorted by tumor tissue. There was erosion of the first rib and of the seventh cervical and first thoracic vertebrae The superior vena cava and azygos vein were compressed The left lower lobe showed bronchopneumonia and pleurisy.

Study of the cases of apical tumors reveals that the correct diagnosis was rarely suspected, much less established, until the disease was far advanced In several instances, the initial chest films were negative and the diagnostic clue to malignancy was the presence of rarefactions in ribs or vertebrae The fact that the initial symptom, pain, is caused by metastatic invasion makes the possibility of early detection very remote under present diagnostic standards

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V

Physical Diagnosis

Despite the importance of the roentgen examination, bronchoscopy, sputum smears, and other means of clinical and pathological investigation, the physical examination plays a definite role in the diagnostic and therapeutic considerations of bronchogenic carcinoma The tendency in recent years virtually to disregard the physical examination in pulmonary disorders is to be deplored Roentgen findings are often equivocal and laboratory data are not always confirmatory A knowledge of physical diagnosis is essential to the complete evaluation of any pulmonary problem Not infrequently the clinical diagnosis of an obscure case of bronchogenic carcinoma is established chiefly on the basis of physical signs

The significance of the physical examination in bronchogenic carcinoma is more fully appreciated when the findings are correlated with the pathological changes produced by the tumor and its metastases The physical signs are considered under two broad categories Thoracic and Extrathoracic

Thoracic Signs

In the majority of patients, at one time or another, physical signs may be elicited compatible with intrathoracic malignancy Many cases have been observed, however, in which physical examination of the chest was completely negative even when the roentgen film showed obvious pathological changes This occurred mainly when there was little parenchymal infection distal to the tumor In about 15 per cent of the patients no significant chest findings can be elicited In general, the thoracic physical signs are caused by (a) the bronchial tumor, (b) infection distal to the tumor, and (c) intrathoracic metastases

Tumor Signs As the tumor grows into the bronchial lumen the inflow and outflow of air is affected in accordance with the bronchial dynamics of respiration The elongation and expansion of the bronchial wall in inspiration tend to nullify the effects of bronchial obstruction, but the opposite expiratory movements exaggerate the narrowing of the lumen The passage of air is impeded in the region of the tumor and a harsh respiratory murmur is heard on auscultation This rhonchus occurs in all types of

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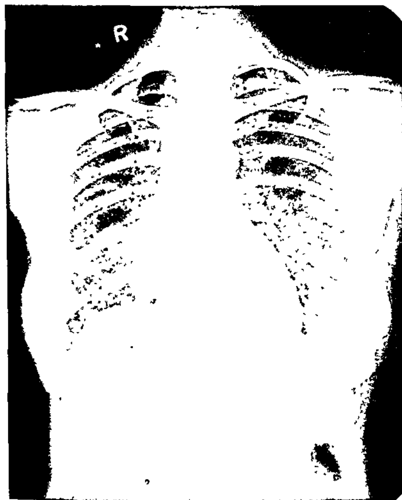
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ciated with little or no dyspnea In most instances of lobar or lung atelectasis some degree of dyspnea is apparent As the disease progresses the corresponding hemi-thorax becomes retracted, the intercostal spaces are narrowed, the diaphragm is elevated, and the trachea is deviated to the affected side. The production of these changes often results in marked



Case Illustration No 1 Patient S V

Fig 1 There is an irregularly defined triangular density in the right lower lobe extending from the hilar region The right hemi-thorax is slightly retracted, and there is narrowing of the interspaces in the lower portion

bronchial stenosis and is not pathognomonic of tumor. It is localized to the region involved and is fairly constant. Rhonchi are often heard very distinctly with the stethoscope while the patient is completely unaware of a wheezing sensation. Bilateral rhonchi are usually associated with chronic inflammatory disease or asthma and have no special significance in the diagnosis of bronchogenic tumor.

Case Illustration No. 1, Patient S. V. (Fig 1)

DIAGNOSIS: Bronchogenic carcinoma, right lower lobe

SIGNIFICANT FEATURES: Clinical picture was that of a viral pneumonia, but localized rhonchus suggested further investigation for endobronchial tumor.

SYNOPSIS. Female, aged 50, returned from ocean voyage with mild respiratory symptoms which persisted for several weeks Roentgen examination disclosed infiltration of right lower lobe, and diagnosis of viral infection was made Patient had a productive cough and intermittent fever but was otherwise comfortable Further study revealed a persistent leukocytosis and elevated sedimentation rate On admission to the hospital the outstanding physical sign was a localized rhonchus heard over the right lower lobe. Bronchoscopy showed stenosis of the superior segment of the right lower lobe, and bronchial aspiration was positive for malignancy.

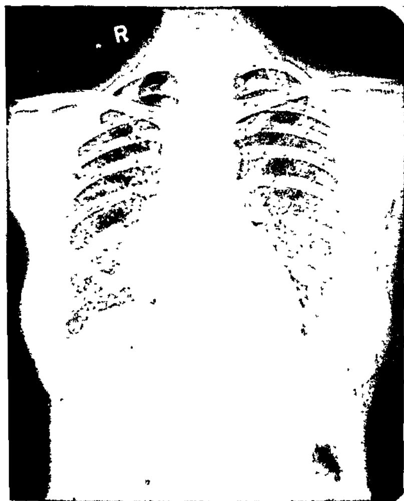
Thoracotomy, three months after onset of illness, revealed an inoperable tumor of the right lower lobe with metastases to the middle lobe and the mediastinal lymph nodes

SURGICAL PATHOLOGY 'Alveolar' type invasion of right lower lobe with involvement of peribronchial and perivascular lymphatics. The mediastinal lymph node specimen was completely replaced by tumor cells

Inasmuch as the vast majority of bronchogenic carcinoma originate centrally (primary, lobar, or segmental bronchi), the localized rhonchus should be elicited in most of the early cases. The fact that this sign is not commonly found (less than 10 per cent) indicates that we are usually dealing with moderately or far-advanced disease. The reason for the disappearance of the rhonchus is evident from the pathological studies As the tumor encroaches upon the bronchial lumen a stage of complete obstruction is eventually reached in which no air passes through the affected bronchus The adjacent lobe or segment becomes atelectatic and the mechanism for production of the rhonchus is no longer present. The routine physical examination of the chest may therefore elicit evidence of bronchial obstruction before atelectatic changes are manifest on the roentgen film In the appropriate age and sex group the rhonchus may be interpreted as a presumptive sign of tumor and should initiate further studies long before other malignant stigmata become evident.

The early effects of the tumor on pulmonary function are determined to a large degree by the location and size of the growth. Complete obstruction of a broncho-pulmonary segment, or even a lobe, may be asso-

ciated with little or no dyspnea In most instances of lobar or lung atelectasis some degree of dyspnea is apparent. As the disease progresses the corresponding hemi-thorax becomes retracted, the intercostal spaces are narrowed, the diaphragm is elevated, and the trachea is deviated to the affected side The production of these changes often results in marked



Case Illustration No 1 Patient S V

Fig 1 There is an irregularly defined triangular density in the right lower lobe extending from the hilar region The right hemi thorax is slightly retracted, and there is narrowing of the interspaces in the lower portion

dyspnea even at rest. In approximately half of our patients dyspnea was a prominent feature, but in many cases multiple factors such as infection, pleural invasion, and mediastinal compression were also responsible.

CASE ILLUSTRATION NO 2, PATIENT B. A (FIG 2)

DIAGNOSIS Multicentric bronchiologenic carcinoma

SIGNIFICANT FEATURES. Abrupt onset of pain, dyspnea, and orthopnea in the absence of previous respiratory complaints, inconclusive roentgen findings despite severity of symptoms.

SYNOPSIS Female, aged 49, suddenly complained of pain over the right lower ribs The pain was of pleuritic type and persisted in association with marked



Case Illustration No 2. Patient B A.

FIG 2 Extending from the right hilum is a small, irregularly defined opacity Adjacent to this area are several linear infiltrations The left lung appears normal

dyspnea Past history negative except for chronic rheumatoid arthritis and menopause at age of 47 Within three weeks after onset, orthopnea was noted as the predominant sign During this interval X rays of chest, spine, gall bladder, kidneys, and gastro-intestinal tract were reported as negative. Two months after onset small bilateral pleural effusions appeared, the right preceding the left by several days Later roentgen studies showed increase of fluid, lymphangitic carcinosis, and osteolytic lesions in the skull, ribs, and pelvis Examination of the pleural fluid was positive for malignant cells

Downhill course was rapid, with new manifestations of metastatic invasion occurring repeatedly Patient died one month after hospitalization and three months after the initial symptoms

NECROPSY Multicentric carcinoma arising from terminal bronchioles of right upper, right middle, and left upper lobe Metastases were found in the pleura, liver, adrenal, and bones

Massive atelectasis is detected clinically by impairment of respiration on the affected side When the condition has existed for some time the thoracic muscles are atrophic and the chest wall is retracted Palpation reveals impairment of fremitus Tracheal deviation to the affected side may be felt but occurs far more often than is recognized clinically The cardiac apical impulse is displaced homolaterally The percussion note is dull or it over the affected region, and if only one lobe is collapsed the resonance of the aerated lobes offers a distinct contrast The breath sounds are markedly diminished or absent

Diminution of breath sounds over a localized area despite normal resonance was mentioned in 1886 by Strumpell as an early sign of primary malignant bronchial disease The clinical significance of this sign in regard to endobronchial obstruction was not generally appreciated for many years Vinson, however, repeatedly emphasized its importance, particularly in association with infiltrative, unilateral hilar densities

CASE ILLUSTRATION NO 3, PATIENT E P (Figs 3 and 4)

DIAGNOSIS Bronchogenic adenocarcinoma, left lower lobe

SIGNIFICANT FEATURES Diagnostic clues were diminished breath sounds and wheezing heard over left lower lobe

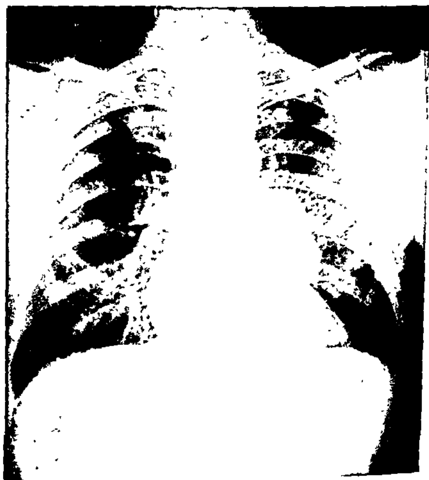
SYNOPSIS Male, aged 59, presented himself for routine check-up, there were no symptoms Physical examination disclosed diminished breath sounds over the left lower lobe associated with wheezing Roentgen studies confirmed suspicion of tumor mass in the left lower lobe

A left pneumonectomy revealed the mass to be located in the superior segment of the left lower lobe and attached to the parietal pleura The mediastinal lymph nodes were involved bilaterally Microscopic studies showed the tumor to be an adenocarcinoma with lymphatic and venous metastases

The post-operative course was uneventful and despite the widespread metastatic findings at operation, the patient was able to resume work two months after resection

SURGICAL PATHOLOGY Primary bronchogenic carcinoma of superior segment of the left lower lobe with lymphatic metastases and venous emboli

Infection Signs Physical examination may reveal evidence of acute or chronic infection distal to the bronchial tumor. In the acute phase the signs are compatible with those of bronchopneumonia, or lobar pneumonia, depending on the location of the growth in the bronchial system Suspicion is directed to the existence of bronchial obstruction when some of the physical signs persist for an unusually long time. Localized dullness and

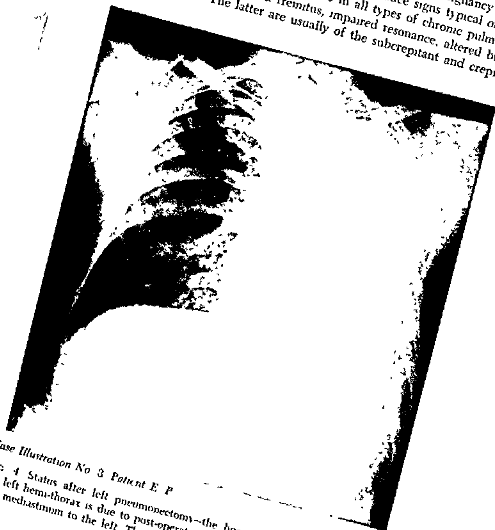


Case Illustration No. 3 Patient E P

FIG 3 There is a large homogeneous density in the left hilar region The periphery of this mass is somewhat irregular and there are linear striations extending into the parenchyma of the left lung The superior mediastinal shadow is slightly widened

crepitant rales may be present even though the roentgen film shows satisfactory clearing

Chronic pulmonary infection is responsible for most of the physical signs present in bronchogenic carcinoma Chronic pneumonitis, bronchiectasis, and pleuritis are frequent concomitants of pulmonary malignancy Bronchiectatic abscesses may be quite large and produce signs typical of cavitation The findings are similar to those in all types of chronic pulmonary infection, namely, diminished fremitus, impaired resonance, altered breath sounds, and rales The latter are usually of the subcrepitant and crepitant



'ase Illustration No 3 Patient E P

c 4 Status after left pneumonectomy—the homogeneous density occupying
: left hemi-thorax is due to post-operative effusion and retraction of the heart
l mediastinum to the left The right side appears clear

variety, but sibilant and sonorous rales are also heard. Amphoric breathing may be present in association with large cavities

Inflammation of the pleura may be regional, producing a flat percussion note in contrast to dullness elsewhere. Encapsulated serous effusion and empyemata are not uncommon When the pulmonary infection extends to the lung periphery, perforation of the pleura may occur. The resulting hydropneumothorax is detected by examining for the characteristic succussion splash.

A source of confusion in interpretation of physical findings is the presence of rales in regions remotely situated from the primary site of the dis-

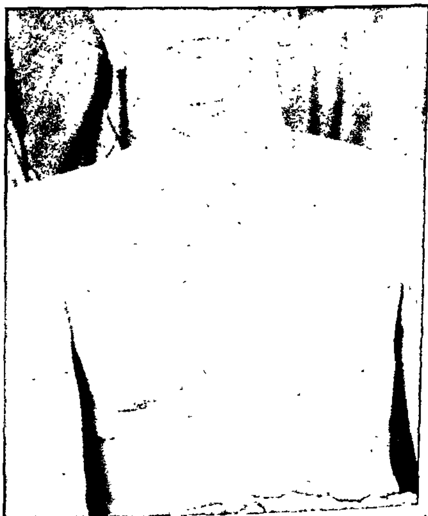


FIG 5 *Distention of Superficial Veins of Chest and Neck in Superior Vena Caval Syndrome*

ease Not infrequently the tumor is diagnosed in an upper lobe and numerous rales are present in the lower lobes. Necropsy studies have explained this by demonstrating evidence of chronic pneumonitis, without tumor, in these regions. The inflammatory changes were apparently the result of bronchogenic spread from the infection adjacent to the tumor

Intrathoracic Metastatic Signs Invasion of the regional lymph nodes, particularly the tracheobronchial and mediastinal ones, may produce a characteristic syndrome from compression of the superior vena cava The chest wall becomes slightly edematous and there is marked distention of the superficial veins of the thorax (Fig 5) There also may be present cyanosis which does not extend below the region of the thorax When examined in bed the patient does not appear to have much difficulty in breathing, but dyspnea becomes very evident on exertion

Homolateral or contralateral rib metastases may be suspected if tenderness is elicited on deep pressure over the individual ribs This type of palpation should be part of the routine examination of the thorax and the findings are sufficiently important to be included in the differential diagnosis of a pulmonary problem There are times when the roentgen shadow is compatible with the diagnosis of apical malignancy or chronic fibroid phthisis In these instances the presence of local rib tenderness would favor the diagnosis of malignancy with rib invasion In order to avoid confusion with the tenderness that results from pleuritis, it is necessary to confine the palpation to the ribs proper and to avoid the interspaces

Case Illustration No 4, Patient H C (Fig 6)

DIAGNOSIS Bronchogenic carcinoma, left lower lobe

SIGNIFICANT FEATURES X ray suggested adrenal tumor, which on necropsy was found to be metastatic from the lung Tenderness over left lower lobe was noted from onset of illness, but significance was not apparent

SYNOPSIS Male, aged 61, complained of dyspnea and pain in the left loin In May 1946 physical examination showed tenderness and diminished breathing over the left lower lobe X-ray studies apparently revealed a left diaphragmatic hernia, to which his symptoms were attributed In December 1946 hematuria was noted, and in February 1947 a mass was palpable in the left flank Pyelography showed the left kidney to be displaced downward These findings pointed to a left adrenal tumor The absence of further changes in the chest X rays precluded serious consideration of an intrapulmonary lesion

On 13 March 1947 the left adrenal tumor was removed but the patient's clinical course continued downhill and he died on 7 April 1947

NECROPSY Adenocarcinoma of tertiary bronchi of the left lower lobe, metastases to ribs, left adrenal, left kidney, liver, right lung, and tracheobronchial nodes

Spread of the tumor to the pleura may result in dyspnea of sudden onset The patient is usually under treatment for a respiratory infection which is apparently subsiding and then abruptly complains of shortness of breath

which becomes progressively more severe. On examination, the affected hemi-thorax lags in respiration and a flat percussion note is elicited The breath sounds are diminished but are audible unless the fluid is massive. The *physical findings* are usually prominent over the lower portions of the lung *because of the* tendency for fluid to form first at the costophrenic sinus and the posterior axillary *gutter. The fluid* may accumulate very rapidly and in some instances appear to occupy the entire pleural space in a



Case Illustration No. 4 Patient H C

FIG 6 At the left base there is a homogeneous rounded density. This had been interpreted as elevation of the diaphragm but was later found to be a tumor mass in the left lower lobe

period of two weeks or even less. The rapid change in physical signs is oft a source of embarrassment to the attending physician who has called in consultant in a suspected case of lung neoplasm By the time the consu tation is arranged the diagnosis has become very evident because of th development of the pleural effusion in the interim

Another thoracic metastatic sign is the presence of a firm subcutaneous mass (Fig 7) attached to a rib or a large portion of the chest wall Ulcera-

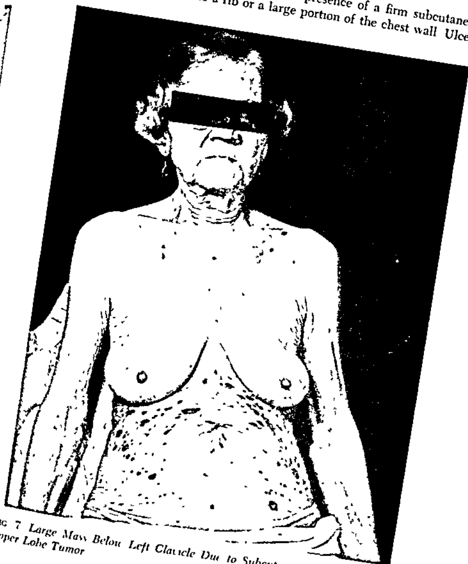


FIG 7 *Large Mass Below Left Clavicle Due to Subcutaneous Invasion of Left Upper Lobe Tumor*



Case Illustration No 5. Patient F A

Fig 8 Throughout both upper lobes there are disseminated nodular and linear infiltrations. The pleura at the right base is thickened In the left upper lobe there is a thin-walled cavity above the hilum. The dense homogeneous shadow overlying the left fourth and fifth anterior ribs represents a large tumor on the chest wall.

tion and necrosis may occur with draining sinuses *Acanthosis nigricans* has also been observed in association with bronchogenic carcinoma

CASE ILLUSTRATION NO 5, PATIENT F A. (Fig 8)

DIAGNOSIS Bronchogenic carcinoma, multicentric origin

SIGNIFICANT FEATURES Coexistent cardiac failure masked the symptoms of carcinoma for three years Diagnostic clues appeared terminally and consisted of (1) evidence of neurological metastases, (2) malignant destruction of ribs, and (3) tumor mass on the anterior chest wall

SYNOPSIS Male, aged 69, with history of four hospitalizations for cardiac failure from 1945 to 1948 The only unusual finding during this period was the presence of linear and nodular infiltrations in both upper lobes These were interpreted as fibrotic changes secondary to vascular congestion Cough, dyspnea, and cyanosis were noted but were accepted as symptoms of cardiac decompensation

On the last hospitalization in May 1948, physical examination disclosed irregularity of the pupils, a bilateral Babinski and a tumor mass on the left anterior chest wall overlying the fourth and fifth ribs X ray revealed the presence of a large cavity in the left upper lobe and destruction of the ribs adjacent to the chest wall tumor

CROPSY. Squamous carcinoma apparently originating from both upper lobe bronchi The possibility of contralateral bronchial metastasis is not excluded Metastatic lesions were present in the adrenals, peritoneum, ribs, brain, and spinal cord.

EXTRATHORACIC SIGNS

Vith few exceptions, such as clubbing or thrombophlebitis, the extrathoracic signs of bronchogenic carcinoma arise from metastatic lesions The recognition of these physical signs is very important not only in regard to diagnosis but also in the determination of operability

CASE ILLUSTRATION NO 6, PATIENT R A B (Fig 9)

DIAGNOSIS Bronchogenic carcinoma, left upper lobe

SIGNIFICANT FEATURES Symptoms suggestive of tumor of five years' duration First disabling symptoms were due to superior vena cava obstruction

SYNOPSIS Male, aged 68, was hospitalized on 15 July 1944 with complaints of cough and weakness of five years' duration One month before admission he noted onset of progressive dyspnea Physical examination disclosed cyanosis of the upper part of the body and neck vein distention Over the upper left half of the chest there was dullness, diminished breath sounds, and coarse rales The X ray showed widening of the superior mediastinum with linear infiltrations radiating from the hilum

The liver was enlarged The blood count showed leukocytosis with 8 per cent myelocytes The clinical impression was lymphoblastoma with metastases to liver and bone marrow Death occurred nine days after admission

NECROPSY *Oat-cell carcinoma, left upper lobe, originating in the apical and posterior tertiary bronchi* Distal to the tumor were small bronchiectatic cavities Metastases were present in the right lung, the tracheobronchial, aortic, and upper abdominal lymph nodes, the kidneys, the duodenum, and the bone marrow. The superior vena cava was stenosed and ulcerated as a result of the glandular compression

Head and Neck. In the examination of the head and neck one looks for cyanosis, edema, and distention of the neck veins as evidence of lymph node pressure in the mediastinum. The eyes are examined for enophthalmos,



Case Illustration No 6 Patient R. A B

FIG 9 The superior mediastinum is widened bilaterally with greater involvement on the left side Linear densities radiate out into the lung parenchyma from the mediastinal masses

contraction of the pupil, and narrowing of the palpebral fissure, and the skin is observed for vasomotor disturbances and other stigmata of the Horner's syndrome (Fig. 10) Positive findings denote invasion of the cervical or upper dorsal sympathetic ganglia The neck and supraclavicular fossae are palpated for enlarged and tender lymph glands The vocal cords are examined with the laryngeal mirror for paralysis indicative of recurrent laryngeal nerve involvement.



FIG 10 *Horner's Syndrome, Right Eye, Associated with Apical Tumor*

Abdomen Careful examination of the abdomen may reveal many signs of metastatic lesions. One looks for distention of the superficial veins, edema of the abdominal wall, subcutaneous masses, and ascites The inguinal regions are palpated for large tender nodes Hepatomegaly is indicative of metastasis, but it must be kept in mind that hepatic enlargement may occur without invasion In our study there was a very high degree of correlation between the clinical and pathological findings in regard to the malignant significance of hepatomegaly Splenomegaly may be due to invasion, but non-specific enlargement was found to be more common Detection of splenic invasion, clinically, is rare Although kidney involvement occurred in a significant number of instances, this was never detected by the physical examination in our series Metastases to the adrenal may on occasion produce a large, firm, tender mass suggesting the presence of a primary lesion Nodular masses in the epigastrium are usually due to peripancreatic adenopathy Pressure on the common bile duct results in jaundice and a very con-

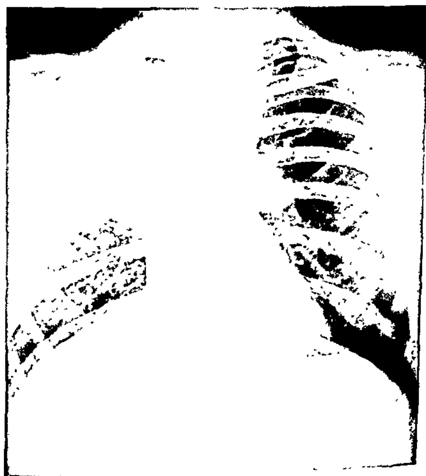
fused clinical picture unless the diagnosis of pulmonary neoplasm has already been established

CASE ILLUSTRATION NO. 7, PATIENT W. Z (Fig 11)

DIAGNOSIS. Bronchogenic carcinoma, right main bronchus.

SIGNIFICANT FEATURES Metastatic carcinoma of liver presenting clinically as chronic portal cirrhosis.

SYNOPSIS Male, aged 46, with history of chronic alcoholism and recurrent episodes of pneumonia. For three years prior to admission he had noted dyspnea and productive cough Examination disclosed the patient to be acutely ill with pneumonic consolidation of the right upper lobe, hepatomegaly, and jaundice.



Case Illustration No 7 Patient W. Z.

FIG. 11. The right upper lobe shows absence of illumination from apex to interlobar fissure Bronchopneumonic areas are present in the left lower lobe.

Laboratory studies revealed moderate impairment of liver function. The clinical picture was that of lobar pneumonia and acute hepatitis superimposed on chronic portal cirrhosis. Malignancy was suspected when the homogeneous density on the X ray showed no signs of resolution despite intense antibiotic therapy.

NECROPSY *Adenocarcinoma of the right main bronchus extending downward into the right middle lobe. The parenchyma of the right upper lobe was not invaded by tumor cells but was the site of an acute lobar pneumonia. Bronchopneumonic lesions were found in the left lower lobe. More than half of the liver was replaced by tumor tissue. Other metastatic lesions were present in the tracheobronchial and aortic lymph nodes, the heart, the kidney, the adrenals, and the pancreas.*

Extremities The upper extremities may show cyanosis, edema, and neck vein distention. The axillae are palpated for adenopathy. A neurologic examination of the extremities should be part of the routine study because of the large number of central and peripheral nerve metastases. Unilateral weakness may be an early sign of invasion and may precede a more obvious paralysis by many months. Muscular atrophy, particularly of the small muscles of the hand, is a diagnostic clue of brachial plexus involvement. The lower extremities should be examined for unilateral edema, atrophy, and abnormal reflexes such as the Babinski and ankle clonus. Jacksonian convulsive movements are an indication of cerebral metastases.

Bones The frequent association of bronchogenic carcinoma with skeletal metastases calls for a complete examination of the osseous structures. The ribs are palpated in the course of the thoracic examination, but usually insufficient attention is given to the vertebrae, skull, and long bones. The vertebral column should be studied in its entirety for local areas of tenderness. Often the location of referred pain will give a clue to the vertebrae involved. In some instances, careful physical examination may detect metastatic osseous foci which are not apparent on the roentgen film.

Clubbing Clubbing of the digits (Fig. 12) is an interesting phenomenon which occurs in many diseases other than carcinoma of the lung. It is often part of a generalized hypertrophic osteoarthropathy. Clubbing has been found in pulmonary tuberculosis, lung abscess, bronchiectases, congenital heart disease, subacute bacterial endocarditis, amoebic dysentery, ulcerative colitis, and acromegaly. The occurrence of this condition in diversified and unrelated diseases has led to considerable speculation about the existence of a common denominator. Many authors have attempted to correlate clubbing with changes in the endocrine glands, particularly dyspituitarism. Fried has described several patients with bronchogenic carcinoma coexisting with acromegaly.

Definite clubbing of the fingers was observed in 10 per cent of our cases. In many others curving of the finger nails was present without enlargement of the terminal phalanges. There was no relationship observed be-

tween the clubbing and either the extent of the pulmonary infection or the size of the growth A few patients presented acromegalic features, but this was not a common finding. The association of clubbing with apical tumors has been noted frequently and in some instances clubbing preceded definite roentgen evidence of tumor. The presence of clubbing may



FIG 12 *Hypertrophic Pulmonary Osteoarthropathy as Manifestation of Bronchogenic Carcinoma*

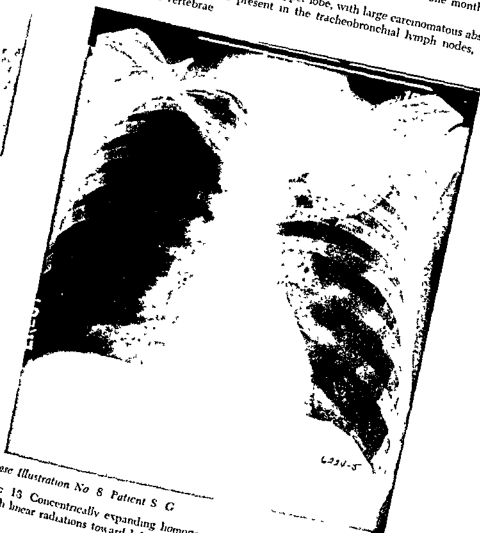
therefore be of great assistance in the differential diagnosis of an apical infiltration

CASE ILLUSTRATION NO 8, PATIENT S. G. (Fig. 13)

DIAGNOSIS Bronchogenic carcinoma, left upper lobe
SIGNIFICANT FEATURES Vague upper respiratory symptoms and left shoulder girdle pain of two years' duration. Diagnostic clue was osseous tenderness
SYNOPSIS Male, aged 56, with history of productive cough of two years' duration. Physical examination was negative except for nasal obstruction and he re-

ceived local treatment in the E N T clinic While attending the clinic complained of pain in the left shoulder radiating down the left arm and w sent to the physiotherapy department He was eventually referred back to th medical clinic where re-examination disclosed marked tenderness over th left upper ribs and upper dorsal spine X ray showed a round circumscribed mass in the left upper lobe On examination in the hospital one month later the mass showed marked concentric expansion

NECROPSY Squamous carcinoma, left upper lobe, with large carcinomatous abscess Metastatic lesions were present in the tracheobronchial lymph nodes, ribs, and dorsal vertebrae



Case Illustration No 8 Patient S G

FIG 13 Concentrically expanding homogeneous round density left upper lobe, with linear radiations toward left hilar mass

Role of the Physical Examination

Since the time of Laennec, very little has been added to our knowledge of physical diagnosis and a great deal has been lost. The value of the roentgen examination, bronchoscopy, and sputum studies has long been established, but the increasing reliance on laboratory procedures has resulted in a corresponding decline in interest in physical signs All too often the physical examination has deteriorated into a cursory performance because of knowledge that an X-ray film is available. The fact that we are no longer solely dependent on the physical examination should not deter us from utilizing this branch of diagnosis to its fullest extent

In bronchogenic carcinoma, the physical examination serves three purposes· (1) to detect the early case; (2) to aid in differential diagnosis, (3) to determine operability

The Early Case. In the program for detection of early cases great emphasis has been placed on the roentgen finding of peripheral lesions in patients without symptoms or signs It should also be realized that peripheral lesions do not account for more than 10 to 15 per cent of the cases. The vast majority of tumors, therefore, arise in the major, lobar, or segmental bronchi and interfere with the normal respiratory dynamics. The degree of interference depends on the size and location of the growth. Cases have been observed in which physical signs of bronchial obstruction preceded roentgen changes, and in all probability this occurs in a great many cases However, unless a careful examination is made, these signs will be overlooked

The localized rhonchus is a most important clue to the existence of bronchial stenosis It does not specify the presence of tumor but always calls for further investigation. When the adjacent parenchymal divisions become atelectatic, impaired fremitus, dullness, and diminished breath sounds are evident Massive atelectasis is generally recognized by marked alterations in respiratory movements and even muscular atrophy of the hemithorax

Crepitant rales confined to a localized area are of diagnostic significance They may be present during an acute infection or following it. Tumors located in the tertiary bronchial divisions may produce pneumonitis in the same broncho-pulmonary segment on several occasions The diagnosis of recurrent or unresolved pneumonia in the approximate age groups should not be made until bronchial tumor has been excluded

Differential Diagnosis It is apparent from Table 1 that most of the physical signs of bronchogenic carcinoma are a result of secondary manifestations or metastases The recognition of the metastatic thoracic and extrathoracic signs is usually of little therapeutic importance but does help in establishing the diagnosis. Before the wide use of bronchoscopy and X ray the meta-

TABLE I. *Summary of Physical Findings in Bronchogenic Carcinoma and Metastases*

SKIN	HEAD AND NECK	THORAX	ABDOMEN	EXTREMITIES
Cyanosis	Horner's syndrome	Dyspnea	Epigastric tenderness	Clubbing
Jaundice	Adenopathy	Cyanosis	Adenopathy	Adenopathy
Intracutaneous nodules	Cyanosis	Venous distention	Hepatomegaly	Weakness
Subcutaneous masses	Edema	Edema	Venous distention	Paralysis
Herpes zoster	Venous distention	Masses	Splenomegaly	Atrophy
Acanthosis nigricans	Vocal cord paralysis	Muscular atrophy	Ascites	Cyanosis
	Tracheal deviation	Respiratory lag	Loin mass	Venous distention
		Osseous tenderness		Edema
		Diminished fremitus		Pathologic reflexes
		Cardiac displacement		Thrombo-phlebitis
		Impaired resonance		
		Altered breath sounds		
		Rhonchi		
		Crepitant rales		

static signs furnished the chief means of detection of pulmonary carcinoma. At present they serve a useful purpose in differential diagnosis.

Before 1920 the recognition of bronchogenic carcinoma was an infrequent occurrence clinically and pathologically. Fishberg in 1921 in a now classic article reported 33 cases of which only 4 were suspected of carcinoma prior to hospital admission, and stated that Symmers had observed but 5 necropsied cases at Bellevue Hospital between 1908 and 1919. The establishment of diagnostic criteria was very difficult and was directed mainly toward differentiating tumor from tuberculosis. The signs due to metastases therefore played a very important part in this process. Among these were diffuse adenopathy, facial and thoracic edema, cyanosis, venous distention, and other pressure phenomena. In the thoracic examination considerable stress was placed on the percussion finding of lobar flatness, particularly in association with altered breath sounds.

The knowledge imparted to us by wide use of the X ray has taught us to be more cautious than our predecessors were in the interpretation of physical signs. Nevertheless, there are many instances when the X-ray findings are equivocal and the physical signs are of the greatest diagnostic importance. Clubbing of the digits favors the diagnosis of neoplasm in cases in which the X-ray film shows small lesions near the hilum or at the apex. While clubbing may occur in many other pulmonary disorders, such as tuberculosis, abscess, or bronchiectasis, it is usually associated with extensive pulmonary involvement. In carcinoma the anatomical extent of the disease may appear to be very small.

Cyanosis of the upper part of the body and venous distention are also more characteristic of neoplastic disease. This is an important differential point in cases that show clinical and roentgen manifestations of tuberculosis or lung abscess. The presence of a Horner's syndrome will often decide the

issue in patients with dense apical lesions or with no apparent pulmonary infiltration. Local rib tenderness and weakness of an upper extremity also yield valuable diagnostic information

Dyspnea or orthopnea in the presence of small pulmonary infiltrations suggests bronchogenic carcinoma rather than benign pulmonary disease

The number of instances of bronchogenic carcinoma erroneously diagnosed as cardiac failure is much larger than is generally suspected The roentgen film is often deceptive in that hilar adenopathy may simulate pul-



Case Illustration No. 9 Patient W. G

FIG 14 The lungs appear normal except for increased hilar markings bilaterally. The transverse diameter of the heart is increased. Original interpretation was enlarged heart and pulmonary congestion.

monary congestion, and metastatic pericarditis may give the effect of cardiac enlargement. The situation is further complicated because of the similarity of symptoms, and because cardiac failure may be a complication of lung cancer. Cor pulmonale due to intrapulmonary lymphangitic invasion or massive direct extension is not rare Thrombo-embolic phenomena involving the pulmonary vessels and direct invasion of the myocardium may also



...se Illustration No 9 Patient W G

...15 Examination in a slightly right oblique anterior position now reveals a ...se mass extending from the right hilar region into the mid-zone portion of ...right lung

occur. Patients in cardiac failure with atypical roentgen or clinical findings merit investigation for pulmonary neoplasm.

Case Illustration No. 9, Patient W. G. (Figs. 14 and 15)

DIAGNOSIS· Bronchogenic carcinoma, right middle lobe.

SIGNIFICANT FEATURES Symptoms, signs, and X-ray findings indicated left ventricular failure on first examination, but further roentgen studies suggested tumor.

SYNOPSIS Male, aged 75, was hospitalized in November 1945 for cardiac decompensation of two months' duration One of his chief complaints was anorexia and he showed evidence of marked weight loss The physical examination revealed an enlarged heart and pulmonary signs of congestive failure The routine postero-anterior X ray showed generalized cardiac enlargement and increased hilar markings bilaterally. An X ray taken in a slightly oblique position revealed a dense mass in the hilar region of the right lung

NECROPSY *Adenocarcinoma of the right middle lobe bronchus at its bifurcation* into tertiary segments. Metastatic lesions were present in the tracheobronchial lymph nodes bilaterally. The enlarged cardiac outline seen on the X ray was due to a pericardial effusion.

Operability. The problem of diagnosis of bronchogenic carcinoma leads directly into the broader one of therapy. The quest for operable cases thus far has been generally unsuccessful. Less than half the patients are considered operable when diagnosed, and in only a fifth can the resection be completed This means that a great many patients have been needlessly subjected to surgery as a result of (1) optimism and (2) inability to detect metastatic foci No physician can work without the former but an effort should be made to correct the latter. A careful physical examination may disclose the presence of metastases which either contraindicate extensive surgical intervention or furnish clues that can be confirmed by other means. Little is accomplished by surgical exploration of patients with widespread metastases that can be detected by simpler measures. The question of operability and metastases is discussed more fully in Chapter x

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VI

The Roentgen Examination

The roentgen examination is indispensable in the diagnosis of bronchogenic carcinoma. *In the majority of cases it furnishes the first clue and in many instances provides the only evidence.* Routine roentgen surveys have given ample proof that lung cancer may attain considerable size without producing symptoms or signs. The marked similarity of clinical manifestations in all pulmonary diseases makes essential the additional information derived from the film *The roentgen examination does not provide the diagnostic proof provided by pathological examinations, but it is often the basis for surgical intervention when biopsies and cytological studies are negative.*

There is no roentgen finding that is typical of bronchogenic carcinoma The more extensive the experience of the observer, the less positive are the conclusions The disease presents a varied picture depending on the site of origin, the size of the tumor, the extent of invasion, and the character of the metastases Nevertheless, there are several patterns which have become sufficiently familiar to evoke immediate suspicion In order to obtain a clear understanding of these patterns it is necessary to correlate the pathological changes in lung cancer with the roentgen findings during the various stages of the disease.

The roentgen manifestations of bronchogenic carcinoma are the result of the following pathological conditions: Endobronchial Obstruction, Parenchymal Involvement, and Metastases.

In some instances, the shadows on the films will represent only one process whereas, in others, the roentgen picture will be a composite of both immediate and remote effects of the tumor. Knowledge of the evolution of these shadows will make it easier to establish the diagnosis at the earliest possible time

Endobronchial Obstruction

Atelectasis In most instances, bronchogenic carcinoma arises from the major bronchi or their lobar divisions *If the tumor is sufficiently large to* obstruct the lumen of the bronchus, the corresponding pulmonary segment become atelectatic. This change is revealed on the X-ray film as a dense

homogeneous opacity, the extent of which is determined by the degree and site of the bronchial obstruction The shadow on the film represents chiefly an airless segment of lung and is not an indication of the size of the tumor itself.



FIG 1 Atelectasis of left upper lobe due to endobronchial obstruction by squamous cell carcinoma The heart and mediastinal structures are retracted to the left.

When the tumor completely obstructs an upper lobe bronchus, the opacity on the film outlines the corresponding lobe and is sharply delimited below by the interlobar fissure (Figs 1 and 2) Obstruction of the lower lobe orifices produces triangular shadows adjacent to the hilar region and extending to the base Lobar atelectasis may be associated with tracheal

deviation, narrowing of the interspaces, and elevation of the diaphragm on the affected side. However, these phenomena are more consistently found in major bronchial obstruction (Fig. 3).



FIG. 2 Atelectasis of right upper lobe due to endobronchial obstruction by bronchogenic carcinoma The trachea is in the mid-line, but the right diaphragm is elevated.

Studies of the segmental divisions of the individual lobes have made it possible to locate, with considerable accuracy, tumors which are confined solely within the lumina of the tertiary bronchi (Fig 4). The lobes of the lung are divided into broncho-pulmonary segments each consisting of a tertiary bronchus and a corresponding section of lung parenchyma Occlusion of one of these bronchi results in atelectasis of the related lung seg-

ment The division of the lung into broncho-pulmonary segments is fairly consistent Some of the classifications vary slightly in the distribution and number of the segments, but all agree on the general design



FIG 3 Massive atelectasis of left lung due to obstruction of left main bronchus by bronchogenic tumor The left hemi-thorax is retracted and the left diaphragm marked elevated The colon is drawn upward into the thoracic cage

The classification of Jackson and Huber is widely used by bronchoscopists and roentgenologists It divides the right upper lobe into apical posterior, and anterior segments, the right middle lobe into medial and lateral segments, and the right lower lobe into superior anterior basal, lateral basal, posterior basal, and medial basal segments The left upper lobe is comprised of two divisions The upper division is divided into apical-posterior and anterior segments The lower division or lingula is divided

into superior and inferior segments The left lower lobe is divided into *superior*, *anterior-medial* basal, lateral basal, and posterior basal *segments*.

The roentgen evidence for bronchogenic carcinoma is in a large measure based on the physiological effects of the bronchial obstruction on the lung *parenchyma with which it is anatomically associated* In cases of lobar obstruction, the homogeneous density produced by a collapsed *lobe is usu-*



Fig 4 Atelectasis of anterior segment of the left upper lobe due to endobronchial tumor In the left lateral view the segment is clearly outlined between the aorta and upper anterior chest wall.

ally easily identified It is also important, however, to recognize the less defined opacities resulting from obstruction of the lobar segments Knowledge of the anatomy of the segments is essential for correct localization on



Fig 5 Atelectasis of superior segment of right lower lobe due to endobronchial obstruction demonstrated by sectional radiography (Tomogram taken about 10 cm from posterior chest wall)

the roentgen film Films taken in the postero-anterior and lateral positions often suffice for segmental localization, but these procedures may have to be supplemented by fluoroscopic studies or sectional radiography (Figs 5 and 6)

The dense homogeneous opacity filling an entire hemi-thorax is a very familiar pattern associated with cancer of the lung On the right side it

usually represents complete obstruction in the main bronchus below the bifurcation; while on the left side a partial obstruction may produce the same picture in the postero-anterior position, but a lateral film may show a considerable portion of a lobe uncollapsed. The roentgen concomitants of massive atelectasis are often observed in major bronchial occlusion These are *elevation of the diaphragm, narrowing of the costal interspaces,*



FIG 6 Left lateral tomogram of same patient shown in Fig 5 The superior segment of the right lower lobe (below arrow) is shown as a narrow dense band extending from the mediastinal structures to the posterior chest wall.

and deviation of the trachea. It is to be observed that elevation of the diaphragm may also be due to interference with the phrenic nerve by enlarged hilar nodes and that enlarged para-tracheal glands may resist tracheal

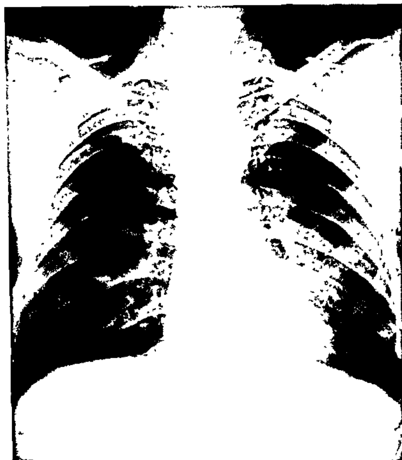


FIG 7A Variations in segmental atelectasis produced by occlusion of left upper lobe bronchus The atelectatic changes are limited to the superior segment of the lingula

deviation, so that the structure remains in the mid-line despite massive collapse of one lung

Throughout the discussion of the roentgen changes in bronchogenic carcinoma it must be emphasized that the shadows produced by atelectasis are the result of obstruction They are not pathognomonic for carcinoma and may be produced by any other type of bronchial occlusion—intrinsic or

extrinsic. Clinical experience has identified these shadows with bronchogenic carcinoma, but the final diagnosis cannot be established on the basis of roentgen findings alone. It should be confirmed by other procedures,

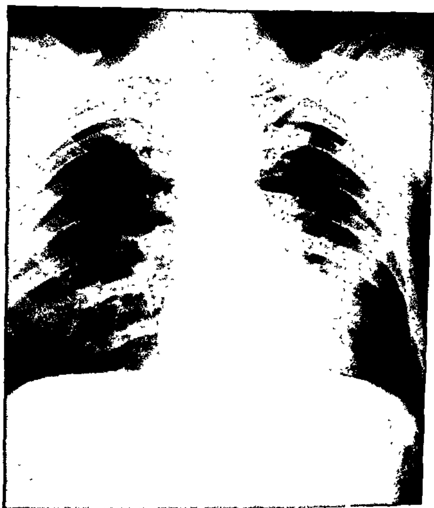


FIG. 7B Three months later, the atelectatic changes are most pronounced in the inferior segment of the lingula.

which may include cytological studies of the sputum, bronchoscopy, and thoracotomy

It may take months and even years of growth for the tumor to completely obstruct a major bronchus The tumor may at first produce atelectasis of only a lobar segment and then gradually increase in size until the entire lung is collapsed Cases have been studied by serial films showing the slow

evolution of the homogeneous density, until it occupied the entire hemithorax (Figs. 7A, 7B, 7C, 7D). Despite the long duration of the disease that usually precedes the production of massive atelectasis, the large homo-



Fig 7C Five months after the previous film, the lingula appears aerated and apical posterior segment is collapsed

geneous density on the roentgen film is often the first indication of bron genic carcinoma

Pneumonitis In addition to atelectasis, bronchial obstruction pro infection in the lung parenchyma distal to the region of obstruction pulmonary infection is recognized clinically as pneumonitis or br pneumonia, depending on the tempo of the process It is recognized

graphically as a localized area of patchy density. Atelectasis and pneumonitis may co-exist in the same part of the lung, but in general one process or the other dominates the picture.

Pneumonitis is most likely to occur when a small bronchus is partially obstructed. Obstruction may be anatomical or it may be physiological, due



FIG 7D Two months later, the entire left upper lobe is atelectatic

to interference with the normal bronchial mechanisms of drainage. Bronchial obstruction of the lobar segments produces segmental pneumonitis, which is usually diagnosed as patchy pneumonia without full recognition of the implications of the process in regard to a malignant etiology (Fig 8).

It is impossible to differentiate clinically between pneumonitis due to bronchial obstruction and an ordinary bronchopneumonia Considerable

information may be obtained by serial roentgen films, however Localization of the inflammatory process to an identified broncho-pulmonary segment, incomplete radiographic resolution of the process long after the clinical



ig. 8 Pneumonitis right lower lobe, distal to undifferentiated carcinoma of osterior basal segment

cal phase of the illness has subsided, and recurrence of the pneumonitis in the same segment at a later date form an important triad in an otherwise innocuous inflammatory process

Segmental pneumonitis may be further investigated by the use of bronchography This is best done under fluoroscopy with a catheter inserted in

the bronchus to be studied In this manner only a small amount of lipiodol need be used, and the chances of an inflammatory reaction are minimized With this technique it is possible to demonstrate the area of bronchial obstruction and bronchiectatic changes in the broncho-pulmonary segments involved (Fig. 9). It should be emphasized that the introduction of lipiodol into the lung may under certain conditions produce an inflammatory reaction. Therefore, if surgery is contemplated in the near future, it would be



Fig 9 Bronchogram showing dilatation of posterior and lateral basal bronchi of left lower lobe distal to localized squamous cell carcinoma.

advisable to omit bronchography and resort to other diagnostic procedures, such as sectional radiography.

Partial obstruction of a lobar bronchus may produce inflammatory changes which closely resemble those of lobar pneumonia, and which cannot be easily differentiated from the latter by the roentgen appearance alone



FIG 10 Large cavity with fluid level in right upper lobe, resulting from central necrosis of anaplastic carcinoma which originated from tertiary bronchi The middle and lower lobes were not involved

Bronchial obstruction should be suspected in all cases of lobar pneumonia where resolution is either incomplete or delayed. Inasmuch as a temporary clinical response to antibiotic therapy may be obtained in penumonitis due to bronchial obstruction, the serial roentgen examination is a far more reliable index to the persistence of the inflammatory process It is not uncommon for patients to appear well on the road to recovery while the X ray shows very little improvement in the extent of the process Cases in this category require a most intensive study before excluding the possibility of bronchogenic carcinoma

The presence of cavitation in a region of lobar consolidation makes it mandatory to include malignancy in the differential diagnosis (Fig 10).

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This is especially true in cases where all the pathological changes appear to be limited to one lung The roentgen appearance of cavitation associated with neoplasm may simulate changes found in tuberculosis and Friedlander's pneumonia Roentgen evidence of unilateral cavitation with absence of tubercle bacilli in the sputum should always lead to suspicion of malignancy. Friedländer's pneumonia usually can be identified by appropriate bacteriological studies of sputum and blood.

Obstructive changes in the lobar bronchi are often followed by anaerobic infection in the lobe The roentgen appearance of consolidation, cavitation, and a fluid level associated with the clinical picture of prostration and expectoration of foul sputum, usually leads to a presumptive diagnosis of putrid lung abscess due to aspiration. It should be recognized that this syndrome may occur in any type of bronchial obstruction—benign or malignant Furthermore, partial closure of the cavity under observation does not imply that the obstruction is only inflammatory. The extent of cavitation is often determined by the dynamics of respiration rather than by actual necrosis of tumor tissue. Subsidence of edema of the bronchial mucosa adjacent to the tumor may alter the pressure changes within the cavity and thereby reduce its size

Obstructive Emphysema. Partial bronchial obstruction may reveal itself on the roentgen film by a localized area of translucency involving that portion of the parenchyma that is supplied by the affected bronchus This is due to emphysematous changes in the alveoli. It is produced by the valvular action of the tumor within the lumen.

If the normal respiratory dynamics of bronchial motion are undisturbed by the tumor, the bronchial wall will continue to dilate with inspiration and contract on expiration. Air is permitted to enter the alveolar structures on inspiration because of the widened lumen, but it cannot leave freely on expiration because the tumor obstructs the narrowed bronchus The resulting rise in intra-alveolar pressure produces the emphysematous changes In order for obstructive emphysema to be present several factors must be favorable, and these include respiratory mobility of the bronchial wall, absence of fixation of the tumor, and the proper relation of pressures proximal and distal to the growth

Parenchymal Involvement

Bronchial Extension. Bronchogenic carcinoma may spread from its site of origin and extend along the bronchial mucosa, eventually invading the lung parenchyma. This may occur at one or several places with complete replacement of the alveolar structure by solid tumor formation The roentgen appearance of parenchymal invasion is that of a dense mass somewhat circular in configuration near the hilar structures Its borders are not confined to segmental or lobar boundaries, and unlike the densities produced

by atelectasis, it tends to expand and invade interlobar fissures The dense shadow may appear as a solid mass or may show areas of rarefaction due to central necrosis within the tumor. Linear opacities radiating from the tumor to the hilar structures are often observed (Fig 11).

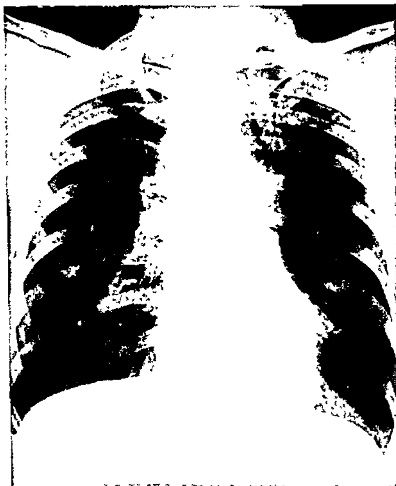


Fig 11 Linear opacities radiating from left hilar region in case of squamous carcinoma of left upper lobe, with metastases to hilar nodes bilaterally.

Abscess Formation Liquefaction necrosis of the tumor mass in the parenchyma produces roentgen changes similar to those of abscess from any other cause The absence of free bronchial communication, however, prevents drainage of the necrotic material, so that the formation of a straight

fluid level line is not a consistent finding. Multiple areas of rarefaction may be the only roentgen evidence of the nature of the underlying process. Sectional radiography may be necessary to supplement the conventional films in order to demonstrate these areas.

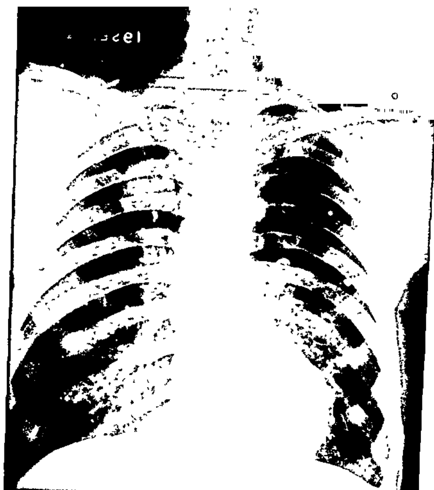


FIG 12 Homogeneous round density right upper lobe due to adenocarcinoma of apical division, right upper lobe, with large abscess distal to the tumor.

Malignant invasion of the lung should be suspected when the roentgen film discloses a dense mass with apparent cavity formation that does not change its configuration during several weeks of observation (Fig. 12). Lung abscess due to bronchial obstruction tends to vary in size, or in the quantity of its fluid contents, in accordance with variations in intrabronchial pressure.

Apical Lesions Tumors arising from the smaller bronchi, or bronchioles, in the apical segments of the upper lobes usually produce supraclavicular opacities on the roentgen film These shadows have a homogeneous density and may vary considerably in size (Figs. 13, 14, and 15). The concentration of bony structures at the apex of the thorax often obscures the presence



Fig 13 Bilateral apical densities due to left upper lobe squamous carcinoma occupying entire upper portion of lobe, and extending to bilateral paratracheal nodes, ribs, vertebrae, and aorta (Horner's syndrome and left shoulder pain were the initial clinical features)

of the parenchymal lesion, so that its visibility is dependent on the degree of expansion and rotation of the ribs It is therefore advisable, in suspected cases, to repeat the roentgen studies using additional techniques such as spot films, sectional radiography, and anterior-posterior films

The recognition of small apical shadows presents a problem in technique and roentgenological experience. The interpretation of these densities with particular reference to carcinoma calls for both a high index of suspicion and a great deal of clinical knowledge of the patient. A small density confined to the apex is usually diagnosed as arrested tuberculosis Its unilaterality may evoke some degree of suspicion, but unless there are symptoms or signs associated with the lesion it will receive little attention Uni-

lateral apical lesions of small or moderate size warrant careful roentgen examination before being dismissed as non-malignant In addition to studies of the lung field there should be detailed inspection of the adjacent ribs and vertebrae for metastases. Apical bronchogenic carcinoma has a tendency



Fig 14 Homogeneous density extending from right hilar region to apex due to oat-cell carcinoma occupying major portion of right upper lobe and extending to mediastinal nodes, bilateral pleural effusion

to metastasize early and rapidly, despite its apparent localization in the lung

The roentgen diagnosis of apical carcinoma may be very difficult for even the most experienced observer. Cases have often been encountered in which metastases to the brachial plexus and cervical sympathetics were quite obvious long before the disease could be recognized radiographically.

There is apparently no relation between the invasiveness of the process

and its size as depicted on the roentgen film At times the film may be interpreted as pleural thickening at the apex while the patient is receiving physiotherapy for weakness in the hand. More complete presentation of clinical data to the roentgenologist might suggest a relation between the

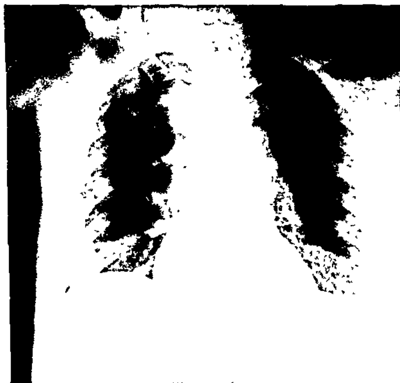


FIG 15 Homogeneous density, mesial aspect of right upper lobe due to circumscribed adenocarcinoma occupving apical region with metastases to right paratracheal and hilar nodes (No pulmonary symptoms, explored for brain tumor because of cerebral metastases)

two conditions on the basis of apical bronchogenic carcinoma. The infrequency with which the latter has been diagnosed in an operable status is of considerable significance and calls for a more thorough investigation of unilateral apical densities

In 1932 Pancoast described a type of apical neoplasm to which he gave the name of 'superior pulmonary sulcus tumor' This tumor was thought to arise within the apical region of the thorax from non-pulmonary tissue Its clinical features included radiographic localization at the apex of the thoracic cage and a tendency to early and diffuse metastases to the bones,

sympathetic ganglia, and brachial plexus. In the succeeding years many cases of 'superior sulcus tumors' were reported. However, further studies discounted the concept that this was a specific entity and recognized the syndrome as an apical form of bronchogenic carcinoma arising from small bronchi or bronchioles.

The difficulties occasionally encountered by pathologists in locating a bronchogenic origin have led to perpetuation of the idea that in certain in-

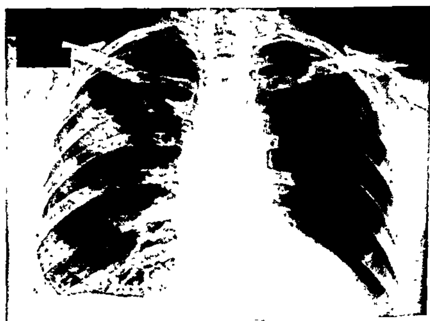


Fig 16 Oval shaped density overlying second right anterior rib due to adenocarcinoma of right upper lobe The tumor was well circumscribed with small area of central necrosis (Courtesy of Dr. Louis E. Siltzbach *Am Rev Tuberc.* 55 170 1947.)

stances the tumor may be of extrapulmonary origin, possibly arising from foetal rests This conclusion does not seem warranted in view of the preponderance of bronchogenic carcinomas found at necropsy, and the increasing ability of pathologists to discover a focus of origin in even the smallest bronchial structure. The term 'superior sulcus tumor' has practically passed into obsolescence but it served a good purpose in dramatizing the recognition of apical cancer radiographically and clinically.

Peripheral Lesions. Bronchogenic carcinoma may manifest itself on the roentgen film as a circumscribed round density near the periphery of the lung field in the postero-anterior position. Other views may locate the density more centrally, or in positions corresponding to the segmental lobar divisions The clarity of the adjacent lung parenchyma enhances the effect

of a sharply delimited shadow even though invasion to other lobes may have already occurred. These lesions usually arise from terminal bronchi or bronchioles and are clinically silent for months, or even years (Fig. 16). Detection is most often the result of a routine check-up or a mass survey.

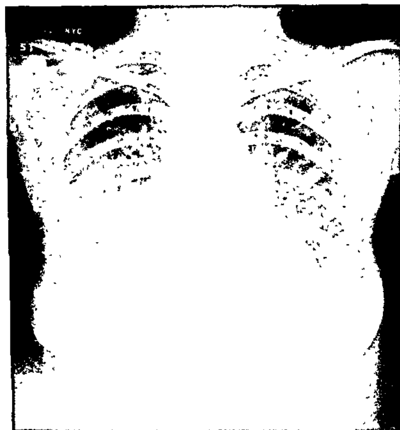


FIG 17 Bronchiologenic (alveolar cell) carcinoma arising from terminal bronchioles of right upper, right middle, and left upper lobes, producing bilateral pleural effusions and infiltrative changes in both lung fields

When peripheral lesions of this type are of considerable size a malignant origin is usually suspected There is a general reluctance, however, to identify the small, nodular shadows, with bronchogenic cancer This presents a serious obstacle to early diagnosis, for the density on the roentgen film is usually the only clue to the existence of the malignant process Patients with small nodular shadows usually have no complaints, the physical examination is negative, there is no sputum to test for malignant cells, and the

location of the tumor precludes bronchoscopic detection The radiographic examination remains the only source of evidence for *long periods of time*, but unfortunately the diagnosis is too often overlooked until the shadow begins to increase in size.

Peripheral densities may be due to causes other than bronchogenic carcinoma Localized interlobar pleurisy, primary tuberculous foci, tuberculomata, metastatic carcinoma, and unresolved pneumonia must be included in the differential diagnosis What is most important, however, is that bronchogenic carcinoma should not be excluded from consideration because of the small size of the lesion or absence of suspicious clinical data

'Alveolar Cell' Tumors. Malignant tumors originating from terminal bronchioles may invade the alveolar structures and encroach upon the alveolar spaces in a manner resembling a pneumonic exudate. The tumor cells line the alveoli in a characteristic manner and until recently the term 'alveolar cell tumor' was used to denote a specific pathological entity originating from 'alveolar epithelium.' (See Chapter II on Pathology for detailed discussion) Formerly considered a rarity, this type of tumor formation has been found in increasing numbers both in surgical specimens and in necropsy studies.

The radiographic manifestations of alveolar cell tumor have been found to follow along three main patterns. The first is that of a localized area of pneumonitis which on serial examination shows no evidence of retrogression. The second is that of a diffuse coalescent mottling resembling lobar consolidation. The third type presents the appearance of nodular dissemination, which may involve one or several lobes and may even be bilateral. The nodular form may appear very bizarre because of associated atelectasis of the intervening tissue (Fig 17). The identification of these nodular lesions with primary lung cancer is most difficult because of the resemblance to miliary tuberculosis, sarcoidosis, secondary carcinosis, pneumoconiosis, and disseminated bronchopneumonia.

Metastases

In a great many instances, the roentgen diagnosis of bronchogenic carcinoma is made on the basis of metastatic foci rather than on the manifestations of the tumor itself. This occurs very often in tumors of the terminal bronchi, but it has also been observed in tumors of the larger bronchi There appears to be no correlation between the clinical duration of the disease and the extent of metastases. Multiple extrapulmonary lesions may be found in cases with brief histories, few symptoms, and small parenchymal infiltrations.

Hilar Nodes Metastasis to the hilar lymph nodes (Fig 18) is a very common occurrence in bronchogenic carcinoma and is found in practically all cases coming to necropsy. The association of a parenchymal lesion with

unilateral, or even bilateral, adenopathy on the roentgen film is strongly suggestive of malignancy, but may be found in other conditions such as pneumoconiosis, tuberculosis, and sarcoidosis It must be emphasized that exaggeration of the normal hilar shadows does not always represent enlargement of the lymph glands, and that, in many instances, surgical ex-

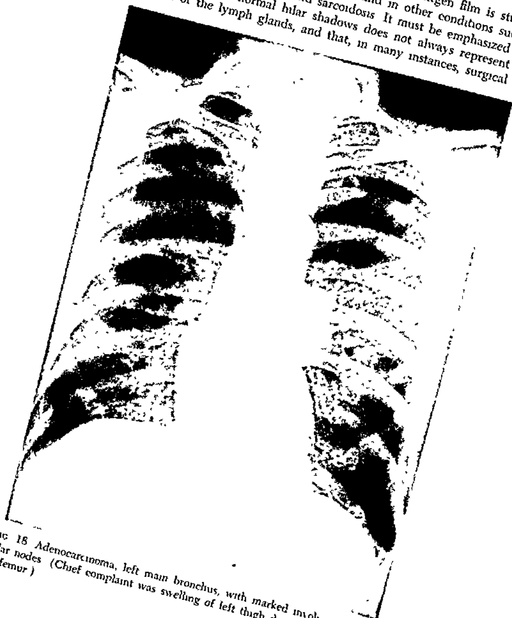


Fig 18 Adenocarcinoma, left main bronchus, with marked involvement of left hilar nodes (Chief complaint was swelling of left thigh due to metastic abscess of femur)

ploration and necropsy have failed to confirm what appeared as *obvious* adenopathy on the X-ray film. It is equally important to realize that the presence of homolateral enlarged glands does not always signify a metastatic lesion from a lung tumor Hilar adenitis due to chronic or acute in-

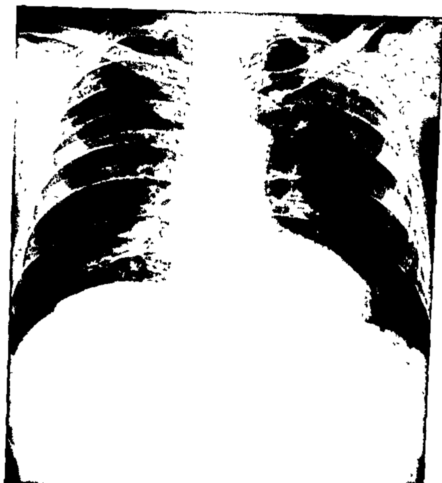


FIG 19 Right hilar adenopathy due to metastasis from carcinoma of esophagus, producing roentgen findings similar to bronchogenic carcinoma

fection may co-exist with a malignant process in the parenchyma. Hilar adenopathy may also represent metastasis from an extrapulmonary malignancy (Fig. 19).

In certain cases, metastatic enlargement of the hilar glands may represent the only roentgen evidence of pulmonary neoplasm. This occurs when the tumor is too small to produce atelectatic changes or when the mediastinal shadow is so prominent that it completely obscures the density produced

by the tumor In the latter case, roentgen studies in the oblique or lateral positions may clearly define a mass that was invisible in the postero-anterior view Fluoroscopic examination is also of great value in differentiation of the components of the hilar shadow.

One of the patterns which occurs with considerable frequency in metastatic hilar adenopathy is that of a semicircular density emerging from the hilum, with the convex surface toward the lung parenchyma It is usually very opaque and may attain considerable size, often completely obscuring the parenchymal lesion Of particular significance in the differential diagnosis of this shadow is the presence of irregularity on the convex surface, with striations radiating out toward the periphery of the lung

Bilateral hilar adenopathy is not uncommon in bronchogenic carcinoma and may simulate the appearance of lymphoblastoma Metastasis to the paratracheal nodes often produces an interesting phenomenon of diagnostic importance. Unilateral apical densities due to old tuberculous foci are usually associated with deviation of the trachea toward the affected side In malignant disease of the apex, the roentgen opacity may resemble tuberculosis but because of homolateral paratracheal adenopathy the trachea remains in the mid-line or is shifted to the contra-lateral side

Bones Metastatic involvement of the ribs, vertebrae, skull, pelvis, and other bones is far more common than is recognized clinically and radiographically As in other instances, the extent of the osseous metastases bears little relation to the size or duration of the tumor In pulmonary problem cases, detailed study of the bones for areas of rarefaction and pathological fractures is most essential The ribs adjacent to the pulmonary density should be given careful study and the routine work-up should include films of the skull, vertebrae, and pelvis

In apical cancer the diagnosis is often made by the finding of osteolytic lesions in the cervical or dorsal vertebra, the upper ribs, or even the scapula and clavicle The pulmonary shadow may be very insignificant in these cases despite the multiplicity of bony metastases In patients presenting themselves with neurological complaints of the lower extremities, destruction of the lumbar vertebrae may be the first clue to the diagnosis

The diagnosis of bronchogenic carcinoma has been repeatedly missed because of the large number of patients whose complaints were entirely non-pulmonary and whose initial X-ray films of the chest failed to disclose an obvious pulmonary lesion All cases with osseous metastases of obscure origin merit serial roentgen studies of the chest

Subcutaneous Tissues Bronchogenic carcinoma may spread to the subcutaneous tissues as a result of metastatic lesions in the bones and superficial nodes. Malignant abscesses are formed which may break through the skin to form draining sinuses The most common sites for subcutaneous involvement are the thorax, the neck, and the inguinal regions, but soft tissue invasion has also been found overlying the femur and scapula Soft tissue

masses have, on occasion, been excised under the impression that they represented primary epithelial tumors, whereas in reality they were metastases from squamous cell bronchogenic carcinomas

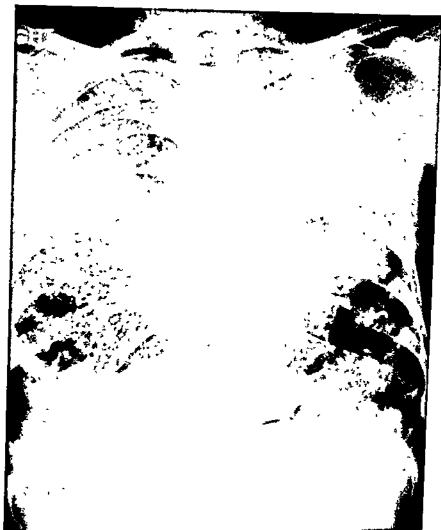


FIG 20 Diffuse nodular infiltrations both lungs with coalescent areas involving left upper and right lower lobes, due to adenocarcinoma with extensive lymphatic invasion

Subcutaneous masses usually appear radiographically as circumscribed, rounded shadows of uneven density. The underlying bony structures should always be studied for areas of rarefaction The presence of a soft tissue mass on the thorax is suspicious of an underlying pulmonary neoplasm The dif-

ferential diagnosis includes tuberculosis and fungus infections such as actinomycosis

Lymphatics Invasion of the lymph channels may produce characteristic shadows which are not only helpful in establishing the diagnosis of lung tumor but also in determining the operability of the case The shadows form a pattern of linear opacities radiating from the parenchymal lesion toward the hilum The streaks are of varying width and may coalesce to form irregular thick strands between the tumor and the hilar lymph glands These opaque streaks are of the greatest diagnostic value in cases where the parenchymal lesion on the film is not easily differentiated, and it is not possible to evaluate the size of the hilar shadow

In the far advanced case, the roentgen picture may show a large round density in the outer zone of the parenchyma, from which radiate thick cords of invaded lymph channels terminating in a globular mass of enlarged glands at the hilum There is usually no difficulty in the recognition of this complex, but it represents a stage of the disease far beyond a therapeutic approach Lymphatic invasion may be very extensive, involving all lobes and producing numerous bilateral densities and hilar masses (Fig 20)

Lymphatic carcinosis of the lung may occur secondarily to primary neoplasms below the diaphragm Carcinoma of the stomach often metastasizes to the lung by way of the lymphatics The streaking in secondary carcinosis is more diffuse and usually bilateral, with the lower lobes showing the greater involvement A further point in differentiation is the absence of a distinct parenchymal density as a source of the radiating strands

Pleura Involvement of the pleura in pulmonary cancer may be either metastatic or inflammatory The latter is the result of infection distal to bronchial obstruction with subsequent extension of the infection to the pleura Perforation of the pleura may occur, resulting in a pyopneumothorax which is usually encapsulated

Pleural effusion due to malignant invasion presents the same radiographic picture as is found in all other effusions (Figs 21 and 22) On occasion, however, there is seen on the upper portion of the curved pleural line a cluster of round shadows giving the effect of scalloping This is a result of multiple malignant implants on the pleural surfaces Malignant perforation of the pleura from extensive necrosis gives the characteristic findings of pyopneumothorax with a straight fluid level line and air above it

The differentiation between massive atelectasis and pleural effusion is not always clearly defined, particularly when both co-exist In general, an extensive unilateral homogeneous density associated with tracheal deviation, narrowing of interspaces, and elevation of diaphragm is indicative of atelectasis and not fluid Massive effusions occur as a result of pleural invasion but not as frequently as suspected Shift of the heart and other mediastinal structures to the contra-lateral side indicates a large collection of fluid En-

capsulated effusions are often very difficult to recognize Extension of the pulmonary process to the pericardium may result in a pericordial effusion which further complicates radiographic interpretation.

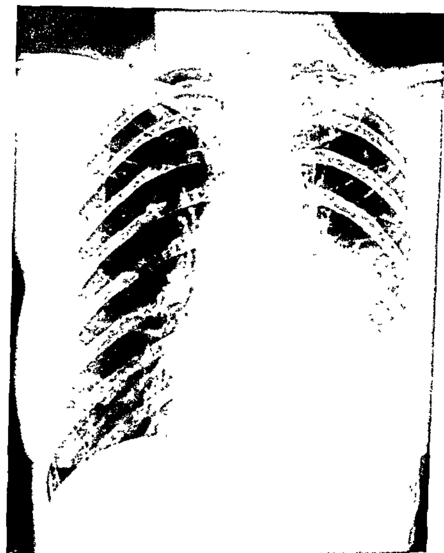


FIG 21 Left pleural effusion due to metastatic involvement from squamous carcinoma of left lower lobe

Small pleural effusions limited to the region of the costophrenic sinus present the greatest diagnostic challenge, because they often represent the first roentgen evidence of bronchogenic carcinoma in an otherwise clear lung field This occurs frequently in tumors arising from terminal bron-

chioles in the lower lobes. In cases with definite respiratory complaints of some duration and negative X rays, subsequent development of a small basal effusion should excite suspicion of lung cancer as the primary disease

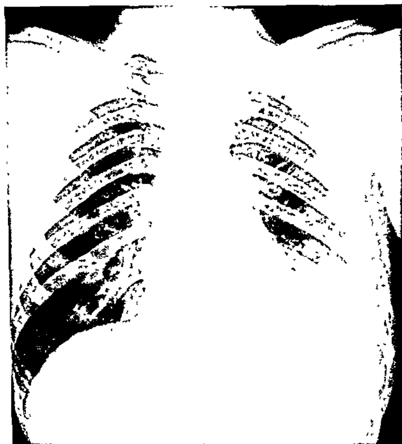


Fig 22 Left pleural effusion due to metastatic involvement from squamous carcinoma of lingula of left upper lobe The parenchyma of both lung fields is negative. The exaggeration of the left hilar markings is due to rotation

Patients have been observed throughout the entire period of clinical illness with no radiographic or other evidence of lung tumor other than pleural effusion, and the correct diagnosis has been established only at necropsy

Clinical observation and laboratory studies play an important part in establishing the identity of pleural effusions Cardiac decompensation, tuberculosis, viral infections, portal cirrhosis, pulmonary infection, and lung

abscess have to be considered in accordance with the data obtained. Metastatic invasion from non-pulmonary cancer must also be ruled out.

Pulmonary Bronchogenic cancer may spread by direct extension, by lymphatic invasion, and hematogenously. The last-mentioned route is prob-



FIG 23 Homogeneous density, right upper lobe, due to papillary adenocarcinoma with multiple discrete and coalescent metastases in both lung fields

ably responsible for the presence of isolated metastatic foci in the contralateral lung and even in adjacent lobes (Fig 23) Intrapulmonary metastases may be single or multiple, vary considerably in size, and are often circumscribed The presence of contra-lateral intrapulmonary metastases often leads to confusion in the identification of the primary lesion

Differential Diagnosis

There are many conditions which resemble bronchogenic carcinoma radiographically In some instances the differentiation may be made by other methods of investigation, but not infrequently the correct diagnosis is established only after surgical exploration The radiographic differential diagnosis of bronchogenic carcinoma may be considered under the following cate-

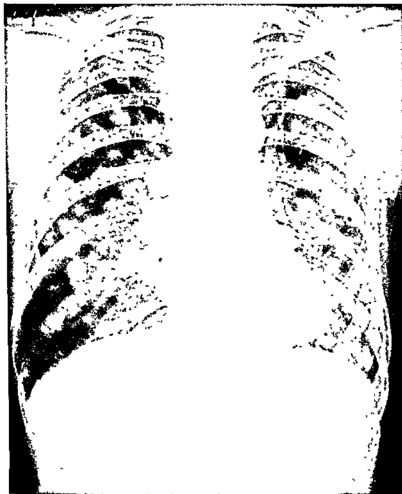


Fig 24 Metastatic infiltrations from carcinoma of esophagus simulating bronchogenic carcinoma with bilateral pulmonary metastases

gories: Secondary Carcinosis; Lymphoblastoma; Benign Tumors, Inflammatory Diseases, Vascular Lesions; and Pleural Effusions.

Secondary Carcinosis The lung is a common site for metastatic foci from non-pulmonary cancers. Tumors of the thyroid, testis, prostate, kidney, salivary glands, and bones frequently involve the lung with the production of multiple, widely distributed round densities resembling snow balls (Fig 24). When these metastases appear as isolated lesions they are indistinguishable from primary lung tumors. Tumors of the breast, stomach, colon, and ovary also invade the lung but usually produce lymphangitic streaking rather than discrete densities. Involvement of the pleural lymphatics is common and results in effusion.

In a five-year study of metastatic pulmonary tumors at the University of Michigan Hospital, Minor found the highest incidence of primary lesions in the breast.

Lymphoblastoma. Hodgkin's disease, lymphosarcoma, and similar tumors produce enlarged hilar densities which are usually bilateral and easily recognized. On occasion, the lymphadenopathy is predominantly unilateral and the roentgen findings resemble those of lung cancer. This similarity is most marked when the enlarged hilar glands press upon a lobar bronchus, producing atelectasis and pneumonitis of the corresponding lobe (Figs 25A, 25B). X-ray therapy may at times serve as a diagnostic test if it produces shrinkage of the glands and subsequent clearing of the lobar density. Hodgkin's disease not infrequently invades bronchial mucosa and the lung parenchyma

Benign Tumors. With few exceptions most benign lesions show no roentgen manifestations of bronchial obstruction. Benign tumors include fibromas, lipomas, myomas, chondromas, and neurogenic tumors (neuromas, gangliomas, and neurofibromas). These growths appear as isolated, dense, rounded shadows and often attain considerable size. Neurogenic tumors are usually found in the posterior mediastinum. They are clearly defined and may attain a considerable size without producing symptoms On occasion extension to the paravertebral regions may occur, producing an hour-glass shape Erosion of the dorsal vertebrae has been noted

Differentiation between neurogenic tumors and apical bronchogenic carcinoma may be very difficult because of the similarities in both the roentgen findings and in the clinical manifestations such as Horner's syndrome, shoulder pain, and muscular atrophy.

Hamartomas may present radiographically well circumscribed discrete densities located either peripherally or deep within the lung parenchyma The presence of calcium deposits may aid in the diagnosis Teratoid tumors may also simulate primary cancer of the lung. The tumor reveals itself usually as a large, clearly defined round mass in the anterior mediastinum, and may show densities suggestive of teeth or bones. Thymomas are also located in the anterior mediastinum in the vicinity of the aortic arch

DIFFERENTIAL DIAGNOSIS

The diagnosis of solitary spherical densities may be very baffling to the roentgenologist The fact that they are very often asymptomatic and revealed only in the course of routine surveys makes them equally puzzling to the clinician In a series of 16 cases of solitary lung tumor studied by Effler, 6 were found to be peripheral bronchogenic carcinoma, 8 were localized tuberculous lesions, 1 was a hamartoma, and 1 was a metastatic nodule

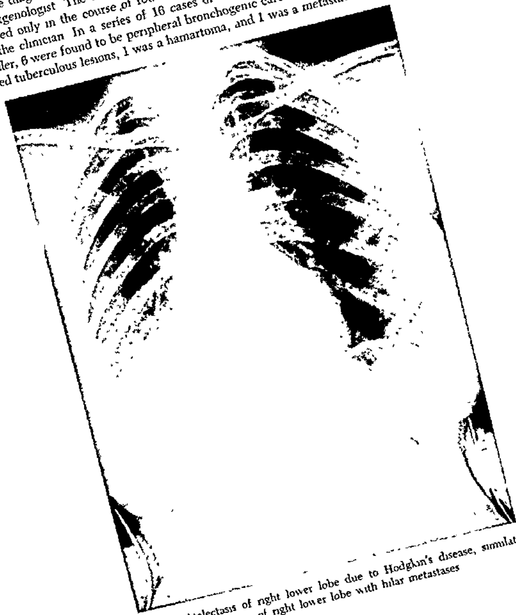


FIG 25A Atelectasis of right lower lobe due to Hodgkin's disease, simulating bronchogenic carcinoma of right lower lobe with hilar metastases

from a hypernephroma removed six years previously. In all cases the diagnosis was established by surgical exploration A series of 24 cases of solitary lung tumor in a younger age group yielded 4 cases of malignancy (Effler, Blades, and Marks). The authors concluded that the uncertainty of accurate diagnosis in these lesions has made surgical intervention the procedure of choice.

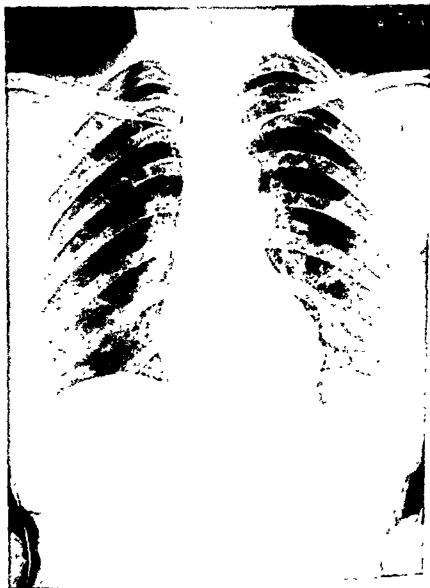


FIG 25B X ray of same patient after radiation therapy showing complete aeration of right lower lobe.

Hemorrhagic cysts may also present radiographically as round densities located peripherally Thinness of the wall and convexity of the fluid level

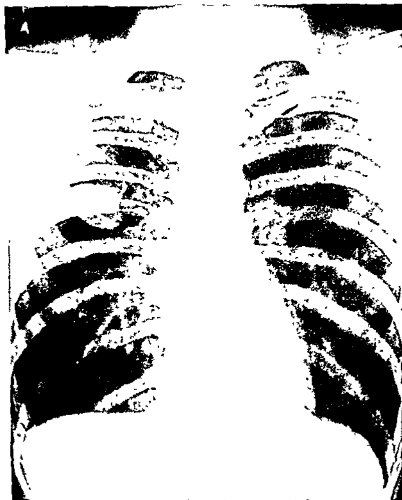


FIG 26 Irregular density, right upper lobe due to hemorrhagic cyst, and simulating peripheral type of bronchogenic carcinoma

are clues which suggest the nature of the lesion and the character of its contents (Fig 26)

Inflammatory Diseases Acute bronchopneumonia, lobar pneumonia, and viral infections of the lung produce densities resembling those of the bronchial obstructive changes in malignancy Unfortunately the more common

error is to diagnose pneumonia when the origin of the lesion is malignancy, rather than vice versa Hilar densities due to pneumonia closely imitate the findings in primary lung tumors.



FIG 27A Density, right lower lung field, due to bronchiectatic atelectasis of anterior segment of middle lobe Clinical and roentgen findings paralleled bronchogenic carcinoma

Subacute and chronic pulmonary infections may also simulate lung cancer. Putrid lung abscess, Friedlander pneumonia, and bronchiectasis produce roentgen changes identical with certain phases of bronchogenic carcinoma (FIGS. 27A, 27B). Fungus infections such as coccidiodomycosis and histoplasmosis may resemble lung cancer when seen in a stage of isolated nodules or cavities.

Pulmonary tuberculosis is probably the most important chronic infection to consider in the differential diagnosis Lungs with solitary non-cavitary



Fig 27B Homogeneous density, right hemi-thorax, with marked retraction of trachea and mediastinal structures due to extensive suppurative pneumonitis and bronchiectasis of right lung

tuberculous foci (tuberculomas) have been excised under the impression that the disease was malignant This has also occurred in cases with blocked cavities. Siltzbach has stressed the presence of streaking, central necrosis, and concentric expansion of the solitary nodules as important differential signs. Unilateral cavitary tuberculosis and tuberculous hilar adenopathy

with extrinsic bronchial pressure may also produce roentgen effects resembling carcinoma.

Co-existence of Lung Cancer and Tuberculosis

The co-existence of bronchogenic carcinoma and pulmonary tuberculosis has provided considerable speculation regarding their etiological relationship. A large number of cases have been reported in the last two decades, but it is very probable that a much greater number remains unreported



Fig 28 *Co-existence of Bronchogenic Carcinoma and Tuberculosis* The density in the right upper lobe is due to a squamous cell carcinoma arising from the right upper lobe bronchus with metastasis to the mediastinal lymph nodes The softer linear shadows in the right first interspace are due to an extensive caseo-fibrotic tuberculosis distal to the carcinoma.

Robbins and Silverman estimate the incidence of carcinoma in cases of tuberculosis as about 1.5 per cent on the basis of 2,900 autopsies. The incidence of tuberculosis in patients with carcinoma as the primary diagnosis has been found more variable, with reports ranging from 2 to 12 per cent Fried found the incidence to be 10 6 per cent in 319 cases of carcinoma The studies at City Hospital showed the incidence of tuberculosis in carcinoma of the lung to be 5 per cent

The roentgen diagnosis of both diseases when they co-exist offers many problems. The chief one is the reluctance to add another interpretation after the primary disease has been established. The diagnosis of a reactivated tuberculosis in a patient with far advanced lung cancer is of little [illegible] a patient [illegible] both dis- [illegible] deter the roentgenologist from interjecting his suggestions of a superimposed malignancy (Fig. 28). Invasion of encapsulated foci may be responsible for the positive sputum

Serial roentgenograms of tuberculosis patients that show evolution of round hilar or parenchymal densities not adjacent to the tuberculous lesions should evoke suspicion of a malignant origin Bilateral apical densities are generally interpreted as fibrotic tuberculosis Concentric enlargement of one of the apical lesions may be due to a peripheral bronchogenic carcinoma Multilocular cavitation is usually associated with tuberculosis, but may also result from endobronchial malignancy. Metastatic foci in the ribs or vertebrae must not be overlooked in suspected cases It should also be realized that nodular bronchogenic dissemination may occur in both tuberculosis and malignancy.

Chronic Granulomas

Sarcoidosis may resemble bronchogenic carcinoma, particularly when the hilar adenopathy is more prominent on one side Involvement of the parenchyma produces an effect similar to malignant lymphatic invasion Large hilar densities, with linear opacities radiating peripherally, may easily be confused radiographically with lung cancer Granulomatous lesions, such as occur in silicosis and other forms of pneumoconiosis, also produce roentgen pictures similar to malignancy. The lesions often present as discrete nodular densities associated with hilar adenopathy Massive conglomeration of the nodular lesions and marked emphysema of both lungs favor the diagnosis of pneumoconiosis rather than carcinoma

Aspiration of mineral oil and other fatty substances may produce chronic granulomatous change in the lungs associated with deposition of the aspirated material (Fig 29) When the changes are localized to a lower lobe, the roentgen findings are very suggestive of bronchogenic carcinoma, al-

though upper lobe paraffinomas may be equally misleading A not infrequent finding is that of a large, dense, consolidated area extending upward



Fig 29 Density, right upper lobe and right para-hilar region, due to lipoid pneumonia of upper and lower lobes (Courtesy of Dr. Milton M. Greenberg)

from the diaphragm The upper surface is irregular and linear opacities radiate toward the hilum. Lipoid pneumonia may also show bilateral confluent patchy densities resembling the roentgen findings in multicentric alveolar cell tumors. Berg and Burford have called attention to the contrast

in density between the sharply defined periphery of the shadow and its feathery hilar aspect

Vascular Lesions It is gradually becoming more recognized that pulmonary infarction may present radiographically in more ways than a tri-

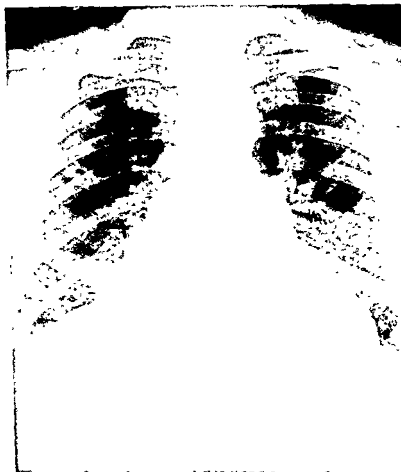


FIG 30. *Circumscribed density right lower lobe and right pleural effusion due to pulmonary infarction secondary to coronary thrombosis*

angular shadow in a lower lobe with the base toward the lateral side of the lung Shadows produced by infarcts vary considerably and include homogeneous densities above the diaphragm resembling effusions, circumscribed round opacities simulating solitary lung tumors, and atelectatic configurations (Fig. 30). Patients with organized pulmonary infarcts have been

resected under the impression that the lesions were malignant. Dilatation of the pulmonary artery may be associated with pulmonary infarction and give a roentgen effect of an enlarged hilar mass In these instances con-



Fig. 31 Frontal angiocardiogram showing occlusion of the right subclavian vein by epidermoid carcinoma of the right upper lobe (Courtesy of Dr. Israel Steinberg. *Am J Roentgen* 64 222 1950)

ventional roentgen film will have the appearance of hilar adenopathy and atelectasis, and be totally misleading as to the nature of the underlying condition It is therefore essential that angiocardiographic investigation be done in cases where the history is suggestive of infarction.

Pulmonary arteriovenous fistulae may produce large round densities which appear very similar to solitary tumors Knowledge of the clinical

features of the case is very helpful in making the differential diagnosis Manifestations such as cyanosis, clubbing, polycythemia, atypical cardiac murmurs, telangiectatic bleeding, and pulsation of the mass are very suggestive of arteriovenous fistula.

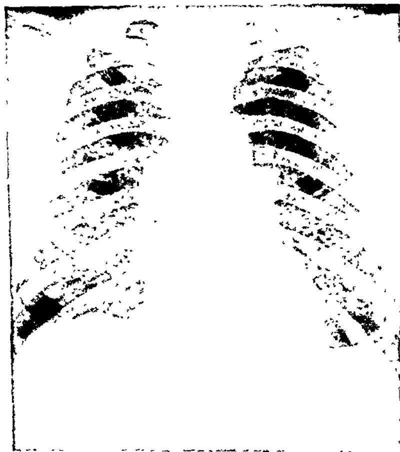


Fig 32 Lung fields negative except for equivocal density in region of right upper lobe near hilum Necropsy examination two months later revealed bronchogenic carcinoma of right upper lobe with extensive extrapulmonary metastases

Large aortic aneurysms involving the arch or descending portion often

diagnosis. Angiocardiograms have also been used in evaluations of operability (Fig 31).

Pleural Effusions. The frequent association between bronchogenic carcinoma and pleural effusion has lead to many erroneous diagnoses of the former condition This is particularly true in cases of long standing or hemorrhagic effusions. Pleural effusions occurring in the course of acute pulmonary infections are common and are usually identified with the underlying condition

Benign or metastatic effusions from extrapulmonary neoplasms may simulate primary neoplasm of the lung Ovarian fibroma and other pelvic tumors have been identified with unilateral and bilateral pleural effusions (Meigs' syndrome). Hematogenous tuberculosis may produce unilateral pleural effusion with scant parenchymal infiltrations Chronic hemorrhagic effusions may be found in conjunction with ruptured emphysematous blebs or in cardiac decompensation Homogeneous shadows simulating pleural effusion and primary intrathoracic disease have occurred in diaphragmatic hernia. Primary neoplasms of the pleura, although rare, must also be considered in the differential diagnosis of lung tumors.

The roentgen examination provides the best diagnostic approach to early bronchogenic carcinoma despite the absence of pathognostic signs There may be very little difference between opacities produced by neoplastic and inflammatory diseases Many conditions must be considered in the evaluation of an obscure density, and the clinical data should be correlated with the roentgen findings In the final analysis, the roentgen interpretation is a composite of symptoms, signs, and shadows

The dramatic effect of the roentgen finding of pulmonary cancer in the absence of symptoms and signs should not eclipse the equally important observation that the disease may produce clinical manifestations without roentgen shadows (Fig. 32). Negative roentgen findings, particularly in the early stages of illness, can give no assurance of the absence of bronchogenic carcinoma. Roentgen studies should be repeated as long as suspicious respiratory symptoms persist

CASE-FINDING SURVEYS

From the therapeutic point of view, the ideal case is the one detected in the course of a routine roentgen examination. The lesion is usually small, there are no obvious metastases, and the patient is asymptomatic This combination of felicitous circumstances favors low operative mortality rates and long survivals The quest for patients in this category has been directed along channels of mass surveys of the population by public health agencies Out of 145 cases with chest abnormalities detected on surveys, Overholt found 35 malignancies All the lesions were resectable and 75 per cent showed no evidence of lymphatic spread This represented an unusually fortunate yield.

The largest mass chest X-ray survey was completed in Los Angeles

County in 1950 with a total of 1,867,201 minifilms Like most of the surveys it was originated for tuberculosis case finding There were 54,648 re-examinations with the conventional 14 x 17 film, of which 3,500 suggested the presence of tumor. According to Guiss, a year after completion of the survey and two years after the onset, about 25 per cent of the tumor suspects were still under investigation The final tabulations showed 222 cases of bronchogenic carcinoma (0 12 per 1,000) of which only 8 (3 6%) were under 40 years of age

Some aspects of the ultimate value of the survey were revealed by checking the deaths from lung cancer in Los Angeles County between 1950 and 1952 with the cases X-rayed In 1950, there were 27 deaths from lung cancer

minifilm as a screening technique for lung cancer, and the necessity for repeated surveys The false sense of security given to the patient on the basis of a negative report must also be considered

A survey of 1,780,178 persons in various localities sponsored by the Public Health Service revealed 1,382 possible tumors (0 8 per 1,000 persons examined). The results are tabulated in Table 1

TABLE 1 *Public Health Service X-ray Survey*

LOCATION OF SURVEY	NUMBER OF EXAMINATIONS	NUMBER OF SUSPECTS	RATE PER 1 000 PERSONS EXAMINED
Savannah-Chatham Co, Ga	67,961	43	0 6
Gaston & Wayne Cos, N C	84,599	58	0 7
Milwaukee Wis	176,469	37	0 2
Minneapolis, Minn	301 513	404	1 3
Washington, D C	439,927	373	0 8
Seattle-King Co Wash	369,129	261	0 7
Tacoma Wash	72,703	32	0 4
Spokane Wash	106,526	67	0 6
Salt Lake Area Utah	162,351	107	0 7
Total	1,780,178	1,382	0 8

The actual yield of lung cancers is far less than the number of suspects The average survey results have ranged between 0 1 and 0 2 per 1,000 persons examined Higher incidence rates are obtained in selected groups. In a Philadelphia survey between 1945 and 1948 the incidence of lung cancer was 0 2 per 1,000 In a special study of 40,607 industrial workers, the incidence was almost 0 5 per 1,000

Scamman analyzed the results of a mass chest X-ray survey in Boston involving 536,012 examinations There were 398 suspicious cases of which 43 were diagnosed as primary cancer of the lung (approximately 0 1 per

1,000 examinations). Twenty-one of the 43 cases were inoperable. Similar results were obtained in a survey in New York City in 1949–50 reported by Bondi and Leites. Out of 228,375 persons examined, 184 were found to have films suspicious of malignant disease. After intensive investigation, the final analysis showed 20 (0 1 per 1,000) previously undiagnosed cases of bronchogenic carcinoma, of which 8 were too far advanced for resection

In a prevalence study of 142,156 persons referred to two official Philadelphia chest roentgenographic units, Boucot and Sokoloff found the incidence of bronchogenic carcinoma to be 30 per 100,000 for the entire group, and 160 per 100,000 for those more than 45 years of age. Among males of more than 45 years, the prevalence rate was 260 per 100,000 The results indicate that the greatest dividends of mass roentgen surveys for lung cancer will be obtained if the group studied is limited to persons over 45 years Of considerable interest in the survey was the finding of a higher prevalence rate among the non-white than among the white males.

Difficulties in the follow-up of the suspected cases makes accurate evaluation of the mass roentgen surveys impossible It is obvious, however, that the number of cases detected in this manner is too small to affect the problem of bronchogenic carcinoma. Most of the mass surveys have had tuberculosis case finding as the primary objective, with the search for lung cancer secondary. Greater selection in the groups studied would undoubtedly yield a higher number of cases.

Routine roentgen examination of all patients in doctors' offices, clinics, and hospitals will reveal many more cases of lung cancer than mass surveys, and at a far less cost. This objective will be achieved by the development of a high index of suspicion on the part of the observer and by close cooperation between clinician and roentgenologist, so that each may profit from the other, and the patient from both

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VII

Bronchoscopy

CHEVALIER L. JACKSON, M.D.

The bronchoscope is, in principle, simply a speculum for obtaining access to the interior of the bronchial tubes. As such it has the same obviously indispensable character of the specula that afford access to other parts of the body. Like other specula, it is bound to be useful in both diagnosis and treatment.

Indications. The indications for diagnostic bronchoscopy in the patient who might have bronchial tumor, benign or malignant, are: cough, hemoptysis, and, especially, some signs of bronchial obstruction as those of obstructive emphysema or obstructive atelectasis. Signs of obstruction must be detected at the earliest possible stage, however, and the concept of the bronchopulmonary segment has favored this. Of course, some lesions begin in the main or lobar bronchus and do not give signs of obstruction until late, but lesions that begin in the segmental bronchi cause segmental obstruction early (Fig. 1), and should be discovered at the segmental stage, even though in the case of malignant tumors total pneumonectomy may be required for a chance of cure.

We have found it convenient to use a topographical classification in analyzing our experience with bronchogenic carcinoma. According to this classification we divide the cases into tumors of the main bronchus, tumors of the lobar bronchus, tumors of the segmental bronchus, and peripheral tumors. In the case of tumors of the main and lobar bronchi, we can generally visualize the lesion and obtain tissue for biopsy. In the lesions of the segmental bronchi and the periphery we can obtain selected secretions from the immediate vicinity of the lesion for cytologic study, and obviously such material is more likely to show the exfoliated tumor cells than sputum. On the other hand, careful sputum studies have shown a fairly high percentage of positive findings also, and certainly sputum should be studied if bronchoscopic specimens are not available or have proved inconclusive.

It should be pointed out at this time that, as stated by the writer many years ago, 'the histologic confirmation of the diagnosis is not the only reason for diagnostic bronchoscopy' The endoscopic appearances of carcinoma of

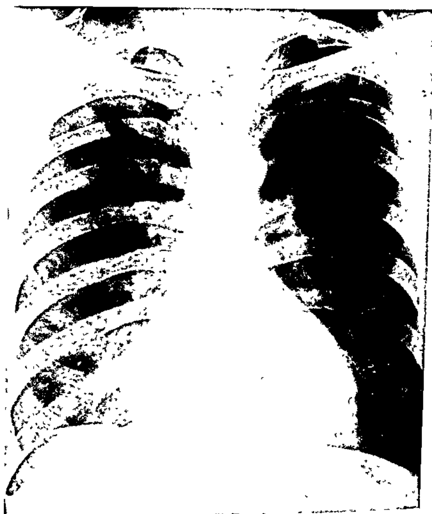


FIG 1 Bronchogenic carcinoma, right lower lobe, arising from posterior basal segmental bronchus and producing segmental atelectasis Positive biopsy obtained bronchoscopically (Jackson, C. L *Ann Otol Rhin Laryngol* 58 1155 1949)

the bronchus were well described in the classic work of Chevalier Jackson (Fig 2), and attention called to the importance of alterations in 'color, form and movement' as observed through the bronchial speculum, or bronchoscope The endoscopic observation of these direct and indirect signs is still important, as well as the confirmation of the diagnosis by biopsy or by exfoliative cytology

In addition to its diagnostic uses, the bronchoscope may be used for aspiration and, in the inoperable cases, for palliative relief of obstruction. In the case of pedunculated adenomas, bronchoscopic extirpation may be curative.

Technique. As stated above, the bronchoscope is in principle merely a speculum, but its use demands proper training in technic to make it safe,

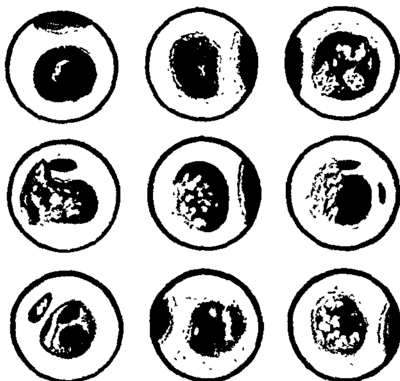


FIG 2 Endoscopic views of bronchogenic carcinoma (Jackson and Jackson *Nose, Throat and Ear*, W B Saunders Co, Phila, 1945)

efficient, and cause as little discomfort as possible. The patient must be placed in the proper position, the instrument grasped in the right hand and, supported and advanced by the bronchoscopist's left thumb, its distal end then passed back over the tongue (Fig. 3) The crest of the epiglottis is visualized through the tube, and the lip of the tube then passed under (or behind) the epiglottis itself, which is lifted forward as the scope is further advanced through the glottis Up to this point the patient's head must be held high, either by an assistant's hand or by a mechanical head rest, and the shoulders kept down. As the tube passes on into the trachea the head is

progressively lowered, and thereafter the position of the head is varied according to the region being examined.

Anesthesia. Bronchoscopy may, of course, be done under general anesthesia; but it is the author's preference to use local, and for the experienced



FIG 3 *Technique of Bronchoscopy* The bronchoscope is introduced directly into the larynx and trachea without the use of the laryngoscope, except in cases of impending asphyxia, or in infants and young children. In such cases, it is best to expose the larynx with the laryngoscope and pass the bronchoscope through it (Jackson and Jackson: *Nose, Throat and Ear*, W. B Saunders Co., Phila. 1945)

endoscopist the advantages are numerous. If local anesthesia is to be used, a spray to the pharynx followed by fractional instillation of the anesthetic solution into the larynx under guidance of the laryngeal mirror has proved the most satisfactory method Premedication is advantageous, especially since the use of a barbiturate helps prevent the toxic effect of cocaine.

Biopsy If the bronchial wall is found roughened or nodular, or if fungating tissue is seen, a small piece should be accurately removed for histologic study If there is only a smooth bulge present, however, an attempt at biopsy is generally contraindicated. The author's preferred forceps for biopsy is the one devised for the removal of ball-shaped foreign bodies This forceps is good because it affords great delicacy of touch, and yet is capable of detaching a suitable fragment of tissue from almost any neoplasm for biopsy In some cases a forceps made like the 'angular cup,' in a bronchial length (Roberts), is more efficacious In any case, tissue removed for biopsy should be handled with great care and placed immediately in formol alcohol solution to prevent drying Reports of histologic study can be obtained in twenty-four hours with the proper laboratory co-operation and the use of the rapid technic Frozen tissue biopsy has been described by Aprighano

Exfoliative Cytology One of the great advances in early diagnosis of bronchial tumors has been the development of the technic of cytologic study by Clerf and Herbut The best collector for secretions to be used for cytologic study is that designed by Clerf This collector is designed to collect with maximum efficiency small amounts of secretion If there is insufficient secretion, washing the suspected bronchus with a small amount of saline is advisable The secretions are smeared on regular microscopic slides and sent to the laboratory for Papanicolaou staining and microscopic study The technic has been described in detail by Herbut Good results have been obtained by the cytologic study of sputum, as stated above, but when bronchoscopic material is available, it should be studied first Clerf and Herbut reported results obtained in a series of 285 proven cases Of these, 253 (88 8 per cent) were diagnosed by cytologic study, while in only 99 cases (34 7 per cent) was bronchoscopic biopsy positive

Operability Despite the higher efficiency of diagnosis in carcinoma of the bronchus and the greatly reduced risks of surgical resection, the percentage of operability is still discouragingly low Bronchoscopic biopsy has been reported positive in from 62 per cent to 89 per cent of the cases in various clinics according to Clerf and Herbut, while few authors have reported more than 10 per cent operability In a series of 269 proven cases seen in the Temple University Hospital, Norris reported that only 12 9 per cent has been found operable We believe that the way to increase the percentage of operability is to see to it that more and more patients are studied by X ray and bronchoscopy at the time of the development of the first sympoms referable to the bronchi and lungs Education of the public and the profession, not only regarding the possibility of cancer, but its curability if diagnosed early is mandatory

Bronchial Adenoma Because the problem of bronchial adenoma is inseparable from that of bronchogenic carcinoma, it is necessary to discuss the role of bronchoscopy in its diagnosis and treatment These tumors most commonly arise in the larger bronchi, and are therefore almost always ac-

cessible to bronchoscopic visualization and biopsy (Fig 4). The indication for bronchoscopy is generally hemoptysis or some sign of bronchial obstruction Diagnosis would be easy if it were not for the somewhat difficult and variable histopathology The writer firmly believes that the crux of the confusion regarding the behavior of these tumors lies in this difficulty of histo-

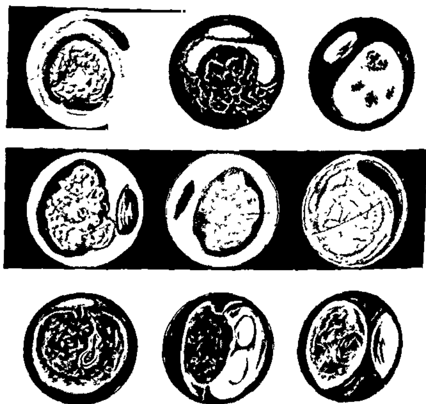


Fig 4 Endoscopic views of bronchial adenoma (Jackson and Jackson *Nose, Throat and Ear*, W B Saunders Co, Phila, 1945)

pathologic diagnosis This view is borne out by the testimony recently published by Carlens in an excellent monograph on the subject. Many a case of adenocarcinoma has been mistaken for an adenoma, and hence the cases of adenoma with distant metastasis found in the literature None of the author's 54 cases has developed metastasis, though some have shown a tendency to invade contiguous structures. The subdivision of adenomas into 'carcinoid' adenomas and adenomas (Figs 5A and 5B) of the 'cylindroma' type, originally suggested by Hamperl, has been adopted by most writers on the subject (Van Hazel *et al*, Jackson and Norris, and Carlens)

As for treatment, there is fairly general agreement that surgical resection is indicated, its extent depending on the location and extent of the tumor

and the condition of the distal portion of the bronchi and the lung In a few of these cases the tumor is pedunculated or attached by a very narrow base, so that it can be removed by bronchoscopic forceps and electrocoagu-



Fig 5A Histological appearance of types of bronchial adenoma A Carcinoid (Jackson, C L and Norris, C M *Dis of Chest* 20 353 1951)

lation In most cases, however, the tumor is extensive enough, and the irreversible changes in the distal structures are such that resection of the lobe or lung is necessary for cure Furthermore, in many cases a large portion of the tumor is extrabronchial Very rarely is pneumonectomy justifiable, however, and it certainly should not be automatically carried out, as in the case of carcinoma In occasional cases, adenomas may be resected by bronchotomy and no lung tissue sacrificed.

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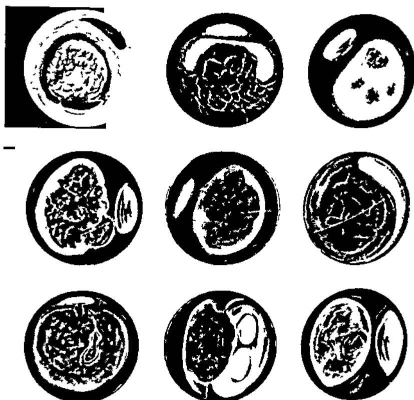


FIG 4 Endoscopic views of bronchial adenoma (Jackson and Jackson. *Nose, Throat and Ear*, W B Saunders Co, Phila, 1945)

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Bronchial adenoma, though considered by some always a potentially malignant tumor (*Graham*), and by others 'borderline' (Jackson and Jackson), is certainly a very different lesion from carcinoma, and of much less



FIG 5B Histological appearance of types of bronchial adenoma B. Cylindroma. (Jackson, C. L and Norris, C M · *Dis of Chest* 20 353 1951.)

serious prognosis Of the author's 54 cases, only 6 have died (2 post-operatively, 2 [cylindromas] of asphyxia, 1 from hemorrhage, and 1 from metastasis from a breast primary). The other 48 are alive and well after various forms of surgical resection some local bronchoscopic resection, some lobectomy, and some pneumonectomy. The author believes it very important make the correct histopathologic diagnosis, then to decide, in the case of a adenoma, what the treatment should be in the particular case

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VIII

Exfoliative Cytology

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Introduction

Exfoliative cytology is playing an increasingly important role in the diagnosis of cancer, particularly in the early stages It is, therefore, not surprising that it should assume great value in the diagnosis and detection of cancer of the lung In this field the method is extremely reliable and for that reason should always be resorted to as a routine step in the examination of patients suspected of harboring pulmonary tumors Growths measuring but a few millimeters in diameter have been successfully detected before there was any other certain indication of their presence, such as shadows on X-ray examination, or lesions visible through the bronchoscope Not only can cancer be accurately diagnosed in about 90 per cent of the cases in which it is present, but its type can be recognized in 80 per cent of these (as proved by a survey carried out on approximately 350 cases in the files of our department at Cornell University Medical College)

In contrast with other diagnostic procedures, the technique used in exfoliative cytology is extremely simple sputum is smeared out on slides, fixed, stained, and examined microscopically All that is necessary is that the patient cough up and expectorate sputum into alcohol, a painless and obviously simple procedure Bronchoscopy is resorted to in order to obtain material from the affected area, or at least from the main bronchi, in succession This becomes mandatory when samples of sputum have been found to be positive for cancer, or suggestive symptoms have persisted long enough to indicate the need for further and more precise localizing tests. The routine examination of smears of sputum is definitely a 'must' in the diagnosis of cases in which there are persistent symptoms of pulmonary disease, it should be just as mandatory as is a search for tubercle bacilli Incidentally, cytologic examination may detect conditions other than neoplastic, since bacterial and mycotic infections may also be discovered by this means

Epithelioid and giant cells exfoliate in tuberculosis, the spores or mycelia of a variety of molds can be detected and, in asthmatic patients, Curschmann's spirals are readily demonstrable.

Technique

Sputum. The first requisite for the cytologic examination is a sample of sputum, which should be the product of a deep cough and preferably obtained the first thing in the morning when the patient arises A shallow cough, or a mere clearing of the throat, will produce nothing more than cells from the upper respiratory tract and pharynx, and will therefore be valueless. The patient should be provided with small, 30 cc. sample bottles filled with 70 per cent alcohol into which the sputum is directly expectorated It is then smeared onto slides in the laboratory. Centrifugation is unnecessary.

Bronchial Aspirates or Washings The examination of sputum alone will not suffice if it has proved to be positive for cancer cells and there are no definite clinical signs as to which lung is involved. To locate a lesion undetectable by physical examination or X ray, it becomes necessary to obtain specimens from the bronchial tree, as well as to inspect it bronchoscopically in an attempt to visualize the tumor. Even should the growth lie beyond the range of vision through the bronchoscope, the presence of blood or pus issuing from the main bronchus of one side, and not from that of the other, will afford a strong indication of the side affected

Bronchial samples are procured by aspirating the secretion through the catheter If the secretion is too scanty to aspirate, 2–3 cc. of normal saline or Ringer's solution can be introduced to wash out the bronchus Care should be taken to avoid contaminating specimens from one bronchus with secretion from the other This is obviously not without its difficulties, but it is possible. Aspirates or washings are mixed with equal parts of 95 per cent alcohol, after rinsing out the collecting tube to obtain as much material as possible They are then centrifuged in the laboratory and the sediment is spread on slides prepared with egg-albumin and glycerol to insure adhesion of the cells to the glass

Fixation Smears of sputum or bronchial specimens are next fixed by immersing the slides for one hour in equal parts of 95 per cent alcohol and ether. They should never be permitted to dry out before this step If they can be left in the ether-alcohol mixture until stained, so much the better, they may remain in it indefinitely without deterioration

Staining Slides are transferred from the fixative to 80 per cent alcohol and run down through 70 per cent and 50 per cent alcohol to distilled water, remaining in each solution until they are clear and transparent. They are then stained for six minutes in *unacetified* Harris' hematoxylin that has been diluted with an equal volume of distilled water. Next they are rinsed in dis-

tilled water, and dipped six times into 0.25 per cent aqueous hydrochloric acid to remove the diffuse hematoxylin stain and to limit it to the nuclei. After this the slides are 'blued' by washing in running tap-water for six minutes. Thus the number 'six' is all that one has to remember in timing the process. Finally they are rinsed in distilled water and run up through 50 per cent, 70 per cent, 80 per cent, and 95 per cent alcohol baths, again with the precaution that they become clear in each bath before being transferred to the next. The nuclei are now precisely stained.

To stain the cytoplasm, the slides are immersed in orange G (OG-6) for 1½ minutes. They are then rinsed in 95 per cent alcohol, usually in two changes, and stained for a like time in cytoplasmic stain (EA-65), after which they are rinsed in three changes of 95 per cent alcohol. It will be noted that these cytoplasmic stains and washes are all alcoholic rather than aqueous; this insures transparency. From 95 per cent alcohol the slides are carried through baths of absolute alcohol, alcohol and xylol (āā), and pure xylol, in which they become progressively more transparent. They are then mounted in any neutral mounting medium under large coverslips. The description of this method may sound complicated but if one has the various stains and solutions ready in glass staining boxes in the proper sequence, it is child's play. The inclusion of orange G in the stain is important as it demonstrates the presence of keratin in the case of epidermoid (squamous celled) carcinomas.

INTERPRETATION

Since the constitution of the cellular content is simpler, the interpretation of smears of sputum or bronchial material is usually relatively easier than it is in the case of other types of smears. Therefore, cells from malignant tumors stand out in bolder relief among the readily recognized normal or merely inflammatory elements. These are comprised of squamous epithelial cells from the oral cavity and pharynx; ciliated, goblet, and undifferentiated reserve cells from the bronchial lining; a variety of leukocytes, chiefly polymorphonuclear, if inflammation be present; phagocytic histiocytes such as 'dust cells,' products of dirty atmosphere, and 'Herzfehlerzellen' laden with hemosiderin and indicative of chronic passive congestion. Aside from these, there is little else save occasional erythrocytes and mucus. Bacterial and mycotic organisms have no resemblance to cancer cells.

Under certain conditions cells may be found that are atypical although not neoplastic. Superficial squamous cells may show some distortion of their normal outline, and they may exhibit variations in the size and density of their nuclei, which may sometimes be very large while their density may approach pyknosis on occasions. There may be sheets of acidophilic, polyhedral cells that suggest slight metaplastic change and may occur in conjunction with chronic bronchitis, or small, ovoid, and bright orange cells with homogeneously distributed chromatin in their nuclei and found under

like conditions. Atypical mucous cells, somewhat resembling parabasal elements but larger, more pleomorphic, and with vacuolated cytoplasm, appear in the sputum of patients with bronchiectasis and may cause considerable anxiety and confusion Lipocytes, found in lipoid pneumonia, are merely fat-engorged histiocytes and are readily identified as such. Occasionally one may observe non-nucleated 'ghost cells,' the significance of which is not entirely clear (Fig I, p 211). They are more numerous in specimens from cancer patients, but they do not in themselves necessarily indicate that cancer is present.

Evaluation of Relative Merits of Specimens of Sputum and Bronchial Material

It should be clearly understood that both sputum and bronchial specimens have their uses. Sputum is an excellent medium in which to find exfoliated cancer cells, because it represents accumulations in the respiratory tree as a whole, rather than elements obtained from a limited area in a bronchus. The fact that sputum represents an off-scouring of a large area, however, explains the occasional overshadowing of neoplastic elements by masses of leukocytes and debris. Furthermore, as has been emphasized, one cannot tell from which lung the cancer cells found in the sputum may have come

Sediments of aspirates are less bulky and present a purer sample of neoplastic cells, but these are spread thinner and require more careful searching before they are detected. Occasionally the smears may be very rich in neoplastic elements, presented in almost 'pure culture' On the other hand they contain numbers of exfoliated epithelial cells from the bronchial lining, and many of these may become readily distorted and thus offer a deceptively neoplastic appearance. The finding of neoplastic cells in the sample from one main bronchus, and none in that from the other, will clinch the diagnosis regarding the side of the system involved

For these reasons it is best to have both types of specimen, and to request repeated examinations over a period of time before being too convinced of the location and malignancy of the growth. Aspirates are widely and thinly smeared, in comparison with smears of sputum, and present an admirable medium in which to study the cytologic characteristics of a given tumor. Because the neoplastic cells are absolutely fresh from their source and undisturbed by manipulation they sometimes afford a better idea of the inherent characteristics of a tumor than do those presented in microscopic sections This is particularly true in the case of anaplastic bronchogenic carcinoma, in which sections show elongated oat-shaped cells with featureless nuclei and burrowing in connective-tissue In smears the cells are almost always spheroidal, seldom oat-shaped, and the nuclei show definite morphologic patterns.

Criteria for Determining Malignant Neoplastic Change

Atypia, metaplasia, anisocytosis, and anisokaryosis, hyperchromasia, clumping of karyosomes, and prominence of the nucleolus, mitotic figures (if very numerous and abnormal), possible thickening of the nuclear membrane—all these may indicate malignant change It is, however, a matter of finding some of these features, for not all of them may be present in one cell Conversely, one of them alone is seldom sufficient evidence for making a diagnosis of malignant transformation A few of the bronchogenic neoplasms exhibit relatively little anisometry, the anaplastic and the bronchial adenoma being examples

Diagnosis of Pulmonary Cancer in General

In diagnosing the presence of malignant tumors of the lungs in smears of sputum and in aspirates, one must first be familiar with the ordinary, non tumorous cellular constituents of such smears We have already described them and stated the criteria necessary for a diagnosis of malignant growths The presence in the smear of sputum of dust cells, or histiocytes laden with particles of inhaled foreign matter, will indicate that it is the product of a deep cough and therefore suitable for examination Aspirations may be assumed to have gone to the bottom of things

First the slide is searched in a cursory fashion for clusters of neoplastic cells, if these are not found it becomes necessary to 'screen' the smear, carrying out a thorough inspection from end to end and side to side of the coverslip, using a mechanical stage to cover every bit of the material In this way single cells are located and recognized as abnormal and hence possibly neoplastic If their appearance is bizarre and abnormal they are readily recognizable as malignant, but if not it becomes necessary to apply the criteria of malignant change to them and to ascertain whether or not the criteria are fulfilled After a while this evaluation is performed subconsciously If there be no doubt as to the presence of malignant tumor, the report is Class v—'conclusive evidence of malignant neoplasm', if there is a slight tinge of doubt the diagnosis is Class iv—'fairly conclusive evidence' If there be definite doubt, but tumor cannot be ruled out and another specimen is desirable, the report is Class iii—'doubtful evidence of malignant neoplasm' If, however, no cells are present that can be considered neoplastic, but there is evidence of metaplasia or other changes that could be attributed to inflammatory reaction, the report is Class ii A smear showing nothing but completely usual and normal elements is rated Class i Having five classes allows leeway for shadings in the degree of certainty of malignant change or the lack of it, some cytologists limit their diagnoses to three classes 'positive,' 'doubtful,' and 'negative' This is largely a matter of opinion

Recognition of Types of Bronchogenic or Pulmonary Cancers

Classification. Nature made the tumor, Man the classification, there is much of the artificial and fallible in a histogenetic classification, but it is the best we can do and it is often useful Although cytologic characteristics can readily be correlated with the various types of tumor, it is highly improbable that a classification of these could be erected on such a basis One could not easily reconstruct the histology of the tumor by observing its cytologic features. In other words, one has the stones but cannot tell what the house looked like.

It therefore becomes necessary to fall back upon a classification based on the histologic features of the growths and commonly used in the discipline of pathology Even here there are pitfalls and at least one of the categories bears closer resemblance to a desk-tray labeled 'unfinished business' than it does to a scientific entity—this is the pleomorphic bronchogenic carcinoma It is quite possible that there is an intergradation between the various types of carcinoma, with the epidermoid and glandular varieties at one end of the scale and the anaplastic at the other. A certain degree of differentiation in a primitive, undifferentiated type would then explain why one tumor is glandular and another skin-like in its composition. Sometimes it is possible to find two or more types in a single section of a bronchogenic carcinoma, one end of the section being predominantly adenocarcinomatous, the other epidermoid

Hence, a classification, as used here, is intended solely as a convenience and a possible indicator of prognosis, for it is agreed that the latter differs with different types. It is possible to identify with a variable degree of accuracy the type of tumor that is exfoliating its cells into the bronchial tree The percentage of accuracy ranges from about 90 per cent in the case of the epidermoid group to 0 per cent in the rarer forms; as the former is the

TABLE 1 *Percentages of Occurrence and Accuracy of Diagnosis in a Series of Pulmonary Tumors*

TYPE	OCCURRENCE (%)	ACCURACY OF DIAGNOSIS (%)	MALES AFFECTED (%)
Bronchogenic carcinoma			
a Epidermoid type	56	90	96.5
b Pleomorphic type	20	70	88.0
c Anaplastic type	12	83.5	83.5
d Adenocarcinoma	12.5	81.5	89.0
e Terminal bronchiolar or alveolar cell type	1.5	0	80.0
f Bronchial adenoma	0.8	0	0.0
Metastatic carcinoma	0.6	75.0 (approx)	66.5
Sarcoma Fibrosarcoma primary	0.2	Recognized as not carcinoma	0.0

commonest, with the rarer varieties representing less than 1 per cent of a series, there is an average over-all percentage of accuracy of 80 per cent for all types

This table will give an idea of the distribution of malignant tumors in a selected series of about 350 well-documented cases in which the diagnosis could be confirmed by the examination of stained sections of the tumors It also indicates which of these offer the best opportunities for accurate diagnosis in cytologic smears, as well as those in which the diagnosis will be missed The figures on incidence by sex are added both for the sake of completeness and because they are interesting

MICROSCOPIC APPEARANCE OF THE VARIOUS TYPES OF PULMONARY CANCER IN SMEARS

Epidermoid Bronchogenic Carcinoma This is the commonest type (often called 'squamous celled') in elderly males Smears of sputum are relatively

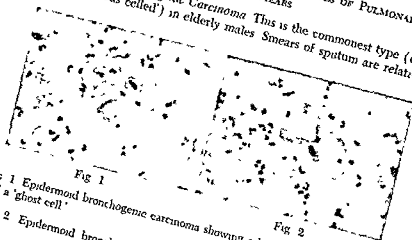


FIG 1 Epidermoid bronchogenic carcinoma showing a keratinized ellipsoidal cell and a 'ghost cell'

FIG 2 Epidermoid bronchogenic carcinoma showing a serpentine keratinized cell

free of leukocytes and debris The outstanding feature is the presence of *keratinized cells*, which have an affinity both for eosin and, more importantly, orange G They may be rather small and ellipsoidal, with a broad cytoplasmic rim (Fig 1), they may become progressively larger until they attain imposing size Their outline, in this event, becomes irregular, so that they are sometimes elongated and serpentine (Fig. 2), or elongated with a bulge at one end (tadpole-shaped) (Fig 3) They may develop several attenuated pseudopodia and resemble octopi In all cases, their nuclei are overstained and dark, standing out prominently from the surrounding cytoplasm (Fig 4) The latter may be finely granular, reticulated, or laminated into concentric rings of keratinized material

When they occur in clusters these may be irregular and resemble bits of distorted epidermis (Fig. 5) or they may be grouped concentrically into epithelial pearls (Fig 6). The latter are more common in the case of



Fig 3



Fig 4

Fig 3 Epidermoid bronchogenic carcinoma showing a large 'tadpole cell' with two non-neoplastic squamous cells (probably of oral origin) in the background

Fig 4 Epidermoid bronchogenic carcinoma showing a small cluster of very large cells showing minimal keratinization and less densely stained nuclei.

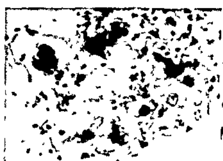


Fig 5

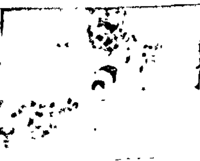


Fig 6

Fig 5 Epidermoid bronchogenic carcinoma showing a cluster of extremely large and irregular keratinized epithelial cells Note the tri-nucleated giant in upper left-hand corner of field

Fig 6 Epidermoid bronchogenic carcinoma showing an epithelial pearl as described in the text

laryngeal and esophageal carcinoma (often diagnosed in sputum) than in that of the bronchogenic, in which keratinization, though present, is less complete and may occasionally be lacking Mitotic figures are only infrequently noted and are of little importance in diagnosis The smaller, ovoid cells first described may be relatively well-differentiated and comparatively

innocent in their appearance, their orangeophilia is, however, so pronounced that it sets them apart from normal constituents of the respiratory system. Non-nucleated ghost cells may abound in smears from this type of carcinoma, but are of value only in so far as they hint that cells more typically diagnostic of malignant tumor may lie elsewhere in the smears. The description of this type of smear will indicate why diagnosis of epidermoid carcinoma is so accurate; its appearance is so typical that it would be difficult to go astray.

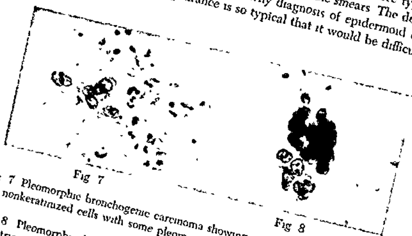


FIG 7 Pleomorphic bronchogenic carcinoma showing an irregular cluster of typical, nonkeratinized cells with some pleomorphism.

FIG 8 Pleomorphic bronchogenic carcinoma showing a thick cluster of fairly isometric cells characteristic of the so-called 'round-celled type.' The thickness of the cluster has interfered with uniform focusing.

Pleomorphic Bronchogenic Carcinoma.* In contrast to the comparatively tidy smears that typify the epidermoid type, those from the pleomorphic variety tend to be dirty, with pus and debris admixed. The tumor cells may be very anisometric and pleomorphic, or they may be large and paradoxically isometric (round-celled carcinoma), according to the variety of the tumor presented (Fig 7). They show no keratinization, have comparatively little cytoplasm in proportion to the nucleus, and do not tend to form pearls or gland-like complexes. The typical cluster (Fig 8) usually consists of a group of loosely associated cells without any definite histologic pattern. In other words, any smear showing malignant cells of variable size and shape that cannot be classed as epidermoid, anaplastic, or glandular in type will probably be best considered to be 'pleomorphic.' This is convenient without being very accurate.

Bronchogenic Adenocarcinoma. As this tumor should always show a glandular architecture in sections, it follows that it should likewise show

* The pleomorphic and the oat-celled types were renamed 'large celled' and 'small celled' anaplastic carcinoma, respectively (International Cancer Congress, 1953).

some evidence of this in smears, but this is not always the case (Figs 9 and 10). Clusters are not as regularly found as they are in the case of the other types, and it is by the presence of vacuoles in their cytoplasm and by their comparative basophilia that they are usually recognized. They may form ring-like groups about a lumen, or the clusters may be solid and without definite pattern. They may also form chains, as though a portion of the lining of a duct had become detached. The smears are comparatively clean and the cells usually harder to find than are those of the other types. On the other hand, should one encounter smears showing abundant clusters of carcinomatous cells exhibiting vacuoles and arranged into solid or glandular



Fig 9 Fig 10

Fig 9. Bronchogenic adenocarcinoma showing a cluster of massed cells, some of which show characteristic vacuoles

Fig 10 Bronchogenic adenocarcinoma showing a cluster of cells of the typical delicate and basophilic variety characteristic of this group

complexes, these probably will have come from cases of metastatic adenocarcinoma primary in some other organ, such as the pancreas or breast

Anaplastic Bronchogenic Carcinoma (oat cell carcinoma). This occurs in a younger age group than do those just described The smears are rather untidy, and at first glance appear to present many lymphocytes. Closer scrutiny proves that these small spheroidal cells are not lymphoid, but epithelial Their nuclei are either precise and rather well differentiated, or they may appear pyknotic and poorly stained (Fig 11). This appearance of faulty technique in a faultlessly prepared smear is typical of the tumor, being even more striking in sections of tissue. The cells usually possess very little cytoplasm, but this varies somewhat In the case of bronchial aspirates they may be rolled up into cylindroids like the cellular casts of renal tubules in urine, but the clusters typical of this tumor are racemose, like bunches of grapes Clusters may be irregular and unevenly outlined While the size of the typical cell is small and uniform, examples of anisometry within narrow limits are sometimes encountered As large numbers of lymphocytes are

rarely found in smears of sputum or bronchial aspirates, it is always well to examine any groups of small cells to rule out anaplastic carcinoma

Bronchial Adenoma ('bronchial carcinoid,' 'oncocytoma'). This rare tumor affords pictures in smears that mislead the cytologist into diagnosing anaplastic carcinoma (Fig 12) Close scrutiny will reveal a more elliptical nucleus with less chromatin than would be found in anaplastic carcinoma, and a cytoplasm that is discernibly granular More work on the technique of differentiating smears of this tumor from those of anaplastic carcinoma should be done, but the difficulty is to get material, among the 4,000-odd cases in our files, there were only three bronchial adenomas

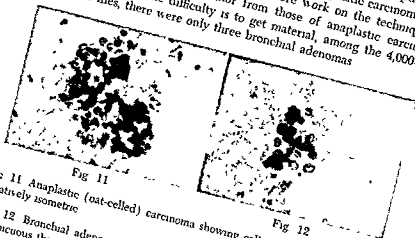


Fig 11 Anaplastic (oat-celled) carcinoma showing cells that are small and comparatively isometric

Fig 12 Bronchial adenoma with cells that are slightly larger and nuclei more conspicuous than occur in anaplastic carcinoma, for which this type is often mistaken in smears of sputum

Terminal Bronchiolar or Alveolar Celled Carcinoma With this tumor, too, there is no difficulty in recognizing it as malignant The smears show scattered cells, or rather irregular groups, in which the elements exhibit vacuolization and a tendency to be multinucleated (Figs 13 and 14)

Other Primary Pulmonary Tumors Sarcomas, such as fibro- and lymphosarcoma, could be identified as such after a little practice, but they are rare and the opportunity for such practice is consequently limited A fibrosarcoma is typified by the presence of fusiform cells, metaplastic fibroblasts, while these can be found in sputum from patients harboring them, the fact that epidermoid carcinomas can produce spindle cells makes diagnosis uncertain Teratomas present the difficulties inherent in their composition, a malignant teratoma in our collection was exfoliating keratinized squamous epithelial cells and not the undifferentiated malignant elements that made it dangerous

Secondary or Metastatic Carcinoma The charactersites of metastatic carcinomas in cytologic preparations have already been discussed under the

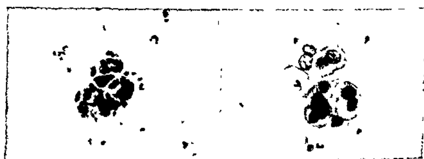




Fig. 13 Fig. 14

FIG 13 Terminal bronchiolar carcinoma showing a cluster of large cells, one of them multinuclear, typifying the tendency of the tumor to form papillary fronds The small black particles are artifacts.

FIG 14 Terminal bronchiolar (alveolar cell) carcinoma showing a single cell with the multinucleation characteristic of the tumor.



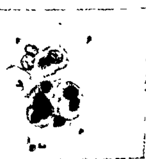


Fig 15 Fig 16

FIG 15 Metastatic pancreatic carcinoma in sputum (Note the crowded massing of cells in the cluster)

FIG 16 Metastatic mammary carcinoma in sputum The morphology is similar to that of primary bronchogenic adenocarcinoma, but in this particular case the cells are larger and the clusters more copiously represented in the smear

description of adenocarcinoma Most of them are adenocarcinomas (Fig 15 and 16) Metastases from tumors of other malignant types, malignant melanoma for instance, can be identified as malignant, but the exact diagnosis of the tumor is another matter.

Primary Pulmonary Cancer in Serous Fluids

After primary bronchogenic carcinomas or metastatic pulmonary carcinomas have progressed to the point where they metastasize all over the

body, serous exudates are often provoked by the clogging of lymphatic drainage, liver damage, or for other reasons Although there can be no thought of early detection in such cases, it is often practical to determine that the exudates present are attributable to carcinoma, rather than to failing heart, cirrhosis, or similar conditions Bronchogenic carcinoma lends itself readily to detection in pleural fluid but rarely invades the peritoneum This is particularly true in the case of the easily recognizable epidermoid form In a special series of 100 serous exudates found positive for malignant growth, bronchogenic carcinoma was correctly identified in 75 per cent of 23 pleural exudates Nineteen of the patients were men and, in the case of men with pleural exudates of this sort, bronchogenic carcinoma was found to be the most frequent invader, with metastatic gastric carcinoma next in line

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IX

Accessory Diagnostic Procedures

Confirmation of the clinical diagnosis of bronchogenic carcinoma cannot always be obtained by bronchoscopic biopsy or cytologic studies of bronchial secretions and sputum In many instances the diagnosis is established only by thoracotomy or by pathologic examination of an accessible metastatic lesion

Examination of Pleural Fluid

Extension of lung cancer to the pleura with subsequent formation of an effusion containing exfoliated cancer cells is common The presence of tumor cells in pleural effusions, however, is not pathognostic for lung cancer because the pleura may also be invaded by sub-diaphragmatic malignancies The fluid may be serous or hemorrhagic The aspirated material is spun down in a centrifuge and the supernatant fluid discarded The button of cellular components is examined by two methods (Figs 1A and 1B)

(1) *Papanicolaou Smear* A small amount of the button is spread on a glass slide and immediately placed in a jar containing a solution of equal parts of 95 per cent alcohol and ether The slide should be immersed in the fixing solution while still moist After fixation for a half hour, or longer, it is stained with the Papanicolaou stain and is then ready for microscopic examination

(2) *Cell Block* The button is fixed with neutral 10 per cent formalin, or some other fixing agent such as Bouin's or Zenker's solution The routine procedures of embedding, cutting, and staining as used in any tissue method are then carried out

Lymph Node Biopsy

Bronchogenic carcinoma invades the intrathoracic lymphatics in almost all instances, and this invasion often extends to the cervical axillary and other nodes Biopsy of a superficial node provides a simple method of establishing the diagnosis, particularly in patients too moribund for bronchoscopy Resection of the deep cervical fat pad and contained nodes has also been

utilized. The excised lymph node is placed in neutral 10 per cent formalin and embedded, cut, and stained for microscopic study (Fig. 2).

On occasion enlarged nodes that appear malignant clinically prove to be only inflammatory on pathologic examination This is of importance in the

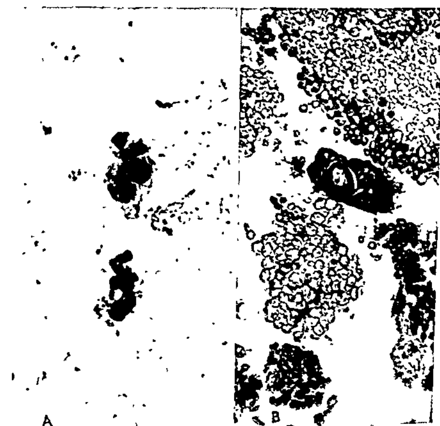


Fig 1 *Pleural Fluid*

A Papanicolaou preparation showing groups of malignant cells

B. The cell block with malignant cells.

[illegible] may repre-

the routine manner

Thoracoscopy and Lung Puncture

Both of these methods have been generally discarded as techniques for obtaining biopsy material and have been replaced by less hazardous and

more accurate procedures Although advocates of the needle biopsy technique claim that the dangers of pneumothorax, hemorrhage, and spread are greatly exaggerated, the procedure is certainly contraindicated in cases under consideration for surgery In most institutions, needle biopsy is done very infrequently at the present time, in contrast to the popularity of the procedure a decade ago The possibilities of tension pneumothorax, air embolism, and intravascular spread of tumor cells are sufficient reasons to

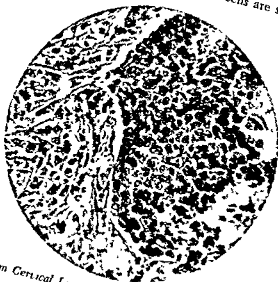


Fig 2 *Section from Cervical Lymph Node Showing Metastatic Squamous Cell Carcinoma*

refrain from needle biopsy in most instances The same hazards are applicable to the induction of a diagnostic pneumothorax for better delineation of the tumor

Hematological Studies

Blood Count Alterations in the blood count have been observed in bronchogenic carcinoma These changes involve chiefly the white blood cells, and although non-specific in character, have proved of considerable value as presumptive evidence In most instances these changes are the result of infection distal to the bronchial tumor, but they may also be due to necrotic changes within the tumor mass or bone marrow metastases

The most consistent finding is leukocytosis The white count may be only slightly elevated or may range between 20–30,000 cells per cubic millimeter Persistent leukocytosis often provides an important clue in patients treated for upper respiratory infections or viral pneumonitis Continuation

of the leukocytosis for weeks after apparent clinical and radiographic recovery suggests the possibility of endobronchial obstruction

Probably the greatest significance of leukocytosis is in patients with continuous or recurrent *respiratory symptoms and negative roentgen findings* during months of observation Tumors arising from small bronchioles may *show no roentgen manifestations* until very late in the course of the disease. The bronchoscopic findings in these instances are invariably negative Despite its non-specificity, the blood picture may provide the only diagnostic clue to malignancy in many obscure cases.

In patients with peripheral nodular lesions in which the differential diagnosis lies between tumor and tuberculosis, *the presence of leukocytosis would* favor the former condition. Localized tuberculous foci are generally associated *with normal white cell counts In carcinoma, central necrosis of the* lesion may be undetected on the roentgen film yet reflect its presence by a sustained leukocytosis.

The differential white count may also be of diagnostic value, particularly in instances of equivocal leukocytosis Associated with the leukocytosis is usually an increase in neutrophils and a corresponding reduction in lymphocytes There is also often present an abnormal number of non-segmented neutrophils, *and a few metamyelocytes and myelocytes. On* occasion, the eosinophile count may go as high as 15 to 20 per cent of the total white count, but *this is not common Most of the eosinophile counts are below* 10 per cent, but when eosinophilia does occur it should be viewed with suspicion unless there is another explanation Eosinophilia of the pleural fluid has also been observed in malignant effusions Increase in the circulating monocytes has been reported in bronchogenic carcinoma

Inferences drawn from the total white and differential counts are based on the clinical evaluation of the patient, and not on absolute hematological criteria These findings are entirely non-specific, but their frequent occurrence entitles them to consideration. Serial blood counts in patients with obscure respiratory symptoms *may yield the first important clue* to the diagnosis of malignancy Abnormally high platelet counts have also been found in cases of lung cancer.

The hemoglobin, red blood cell count, and color index show no significant changes in this disease In a large series of cases the number of patients with and without anemia is about equal It is unusual for patients in the early stages to show any evidence of reduction in red blood cells or hemoglobin. The absence of anemia has also been observed in far advanced metastatic disease and in pre-terminal states.

Sedimentation Rate. Rapid sedimentation of erythrocytes is found in a great man [illegible] conditions In bronchogenic carcinoma, [illegible] Necrosis of tumor tissue and [illegible] or elevated rates

But normal sedimentation rates are also encountered, and they emphasize the discretion necessary in the evaluation of the test.

Like the white blood count, the sedimentation test gives no absolute values and must be correlated with the clinical and roentgen findings Not infrequently rapid sedimentation is found without leukocytosis, or precedes it, suggesting greater sensitivity In the obscure pulmonary problem, a normal sedimentation rate is of no diagnostic help, but an abnormal rate indicates latent infection or tumor Retrospective analysis of many cases of bronchogenic cancer has revealed persistently rapid sedimentation months before roentgen evidence was visible Likewise, during remissions between episodes of pneumonitis due to endobronchial obstruction, the sedimentation rate remains elevated despite the disappearance of clinical manifestations of disease

Tests for Metastases The great discrepancy between resectability rates and the large number of patients considered suitable for surgery is obvious proof of the difficulties in the clinical diagnosis of metastases

The tracheobronchial lymph nodes are the site of the greatest metastatic involvement, but unless there is roentgen evidence the diagnosis is usually not made until surgical exploration The ribs, vertebrae, and other bones also show a higher degree of metastasis than is recognizable radiographically or clinically Spread of the tumor by extension, or by lymphatics, plays such a prominent part in the clinical course of the patient that it is not generally realized that hematogenous dissemination also occurs Involvement of the liver, adrenal, kidney, and other viscera is commonly found at necropsy

Diagnosis of latent metastases is generally limited to radiographic techniques, namely serial section radiography of the lungs, or Bucky films of the bones The frequency of metastases to the liver and bones has suggested that tests designed to ascertain functional abnormalities of these tissues might have some usefulness in the detection of metastatic foci

Bone Marrow Studies

Aspiration of the bone marrow may yield definitive evidence of metastasis the finding of tumor cells or, presumptive evidence, by the presence in the smear of cells indicative of hyperplasia of both myeloid and erythroid elements Metastatic involvement of bone may also result in a myelofibrosis and hypoplasia of the cellular elements The simplicity of the procedure should warrant its inclusion in the study of problem cases.

Liver Function Tests

The cephalin flocculation and thymol turbidity tests are used to determine hepato-cellular damage Metastatic involvement, however, may be very extensive without producing significant alterations in the flocculation tests

Normal cephalin flocculation and thymol turbidity reactions are therefore of little diagnostic value In the interpretation of positive reactions a history of previous hepatic damage should be excluded

Significant elevations of the alkaline phosphatase have been observed in cases with metastases to the liver and bone marrow. Prolongation of the prothrombin time has also been found in association with liver metastases. Increase of the serum bilirubin may be caused by direct involvement of the liver or by obstruction of the bile ducts by metastatic lymphadenopathy. Sub-clinical jaundice is not an uncommon finding

The high percentage of liver metastases found on necropsy makes it desirable to include in the work-up of the case determination of the serum *bilirubin, alkaline phosphatase, prothrombin time, and one, or more, flocculation tests* Mendelsohn and Bodansky subjected a series of patients with various malignancies to a variety of liver function tests and concluded that the serum alkaline phosphatase was the only test that was of aid in the diagnosis of metastatic liver disease when the condition was not advanced

Serodiagnostic Chemical Tests

An accurate biochemical test for cancer would solve many of the diagnostic problems confronting the clinician, but no procedure introduced thus far has proved satisfactory

Interest in the subject was revived in recent years with the introduction of several new tests. Among these are the methylene blue reduction time, the heat turbidity index, the iodo-acetic acid index, and the mucoprotein fraction blood level. While the results showed a high percentage of positive reactions in cancer patients, the accuracy was not sufficient to warrant the inclusion of these tests as diagnostic procedures for cancer. Hill, Stowell, and Mulford evaluated tests for cancer on a series of over 500 persons. The procedures utilized were the plasma-heat coagulation, methylene blue reduction, Roffo neutral red, and Munro protective colloid tests The results showed that 24 to 36 per cent of the patients without malignancy gave a positive reaction to the four cancer tests, whereas only 32 to 45 per cent of the cancer patients had positive tests

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X

Surgical Therapy

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Introduction

It is now an established fact that bronchogenic carcinoma can be cured by surgical resection In 1933 a physician with primary carcinoma of the lung encouraged Dr Evarts Graham to remove his lung The operation was successful, and the patient continued his medical practice for more than twenty years In the next five years (1933–8) pioneers in thoracic surgery occupied themselves with technical details of surgical resection, because the surgical procedure was often complicated by the development of a bronchial fistula and a subsequent empyema Only a few five-year cures were reported during this period, and some of those included bronchial adenoma, erroneously considered as carcinoma During the years 1938–43, while World War II was going on, there was a steady improvement in surgical results In the next five years (1943–8), the thoracic surgeon was far better armed He had greater surgical experience, better anesthesia, organized blood banks, antibiotics, and a new team-mate, the clinical physiologist, to help him combat the rapidly growing problem of lung cancer

Though 1948 marked fifteen years' experience in the surgical treatment of bronchogenic carcinoma, it required another five years (1948–53) to analyze in detail the factors responsible for the successes, or more important, the factors responsible for the failures In brief, it has become apparent that at the present time technical advances have arrived at the point where surgical skill eclipses diagnostic acuity If necessary, the lung, parietal pleura, part of the chest wall, some of the trachea, the mediastinal lymphatic system the pericardium, and part of one auricle can be resected in the effort to obtain a 'cure' Yet the dimensions of the operative procedure, and the taxation on surgical skill, could be remarkably reduced by an early diagnosis Refinements of present surgical techniques will not significantly alter the

future results. The only hope for improvement, in the light of our present knowledge, is an early diagnosis made by an alert medical profession

Results of Surgical Therapy

General Considerations. The surgical treatment of lung cancer during the past two decades has been mostly a salvage operation Only a small percentage of the cases diagnosed have been found suitable for resection, and the vast majority of the resectable cases have had obvious metastases at the time of operation. In a collected series of almost 15,000 cases (see Chapter I) the average incidence of operability was 33 per cent and the incidence of resectability was 18 per cent The majority of the resections were palliative procedures.

The group of surgically treated patients with the expectancy of cure or long-time survival is limited to the resected cases without metastases This represents about 25 per cent of the resected group, and less than 5 per cent of the total cases diagnosed. In a few instances, patients with involved lymph nodes have survived for many years after resection, but these cases are outstanding exceptions Certain selected series have shown the incidence of resectability and non-metastatic disease to be considerably higher than the average, but this has not significantly altered the over-all picture.

Survival Rates The best results of surgical therapy thus far show a five-year survival rate of from 20 to 25 per cent of the resected cases This represents a very small fraction of the total cases diagnosed and is an indictment of the inability to diagnose noninvasive cancer. One of the most discouraging aspects of surgical therapy has been the relatively unchanged incidence of resectable patients during an era in which so much progress was made in the development of surgical technique. In certain clinics the incidence of resectability became higher in the past decade, but this was often a manifestation of increased surgical skill rather than of increased minimal lesions

Throughout the various clinics in the United States and abroad, the percentage of far advanced cases is just as high as it was in the early days of thoracic surgery, because the diagnosis is still largely established on the basis of invasive manifestations As a result of roentgen surveys, a number of cases have been detected in an asymptomatic state, but not all of these were resectable However, the number of noninvasive cases diagnosed by survey screening has been far too small to affect the total results

Resectional surgery will continue to be an essentially palliative measure until the ability to diagnose noninvasive cancer becomes generally manifest The proper evaluation of surgical results must, therefore, be restricted to consideration of the cases without metastases In general, the five-year survival rate has been found from three to four times higher in cases with the disease confined to the lung Nevertheless, some patients with obvious

metastases at the time of operation have shown a surprisingly high incidence of survival beyond the normal expectancy

Statistical Reports * The ultimate surgical results in any clinic are determined by many factors exclusive of surgical technique These include (1) percentage of noninvasive cases, (2) criteria for selection of patients for exploration, (3) attitude toward resection of metastatic cases, and (4) histological type and grade of the tumor The number of long-time survivals may depend on any, or all, of these factors

Gibbon reported on 380 patients explored at the Jefferson Medical College Hospital between 1946 and 1953 There were 205 resections (54 per cent of the explored cases and 39 per cent of all cases observed) with an operative mortality of 22 per cent In 34 cases, operative death was due to errors of technique or management, and in 11 cases to cardiovascular complications There was a distinct association between the extent of involvement of the tumor and the operative mortality The five-year survival rate was 22 per cent of the resected cases and 9 per cent of the entire series There was a high death rate in the first two post-operative years, but after that the rate paralleled the survival curve of the normal population of similar age group The survival rate of the cases without metastases was four times that of the cases with extension

Churchill was able to resect 171 cases (58 per cent) out of 294 subjected to thoracotomy at the Massachusetts General Hospital betmeen 1930 and 1950 There were 114 pneumonectomies with an operative mortality of 22 8 per cent, and 57 lobectomies with an operative mortality of 14 per cent Comparison of the results obtained before 1948 with those during the period 1948 through 1949 revealed that the operative mortality was 28 7 per cent for the 87 pneumonectomies before 1948 and only 3 7 per cent for 27 pneumonectomies in the later period In regard to the lobectomies, there were 31 operations before 1948 with an operative mortality of 22 6 per cent and only 1 death (3 8 per cent) out of 26 operations in 1948 and 1949 The five-year survival rate for the pneumonectomy cases was 20 per cent, and for the lobectomy cases 25 per cent

The presence of involved lymph nodes significantly affected the chances of long survival The patients without lymph node invasion had a five-year survival rate of 34 per cent, whereas there were no five-year survivors with positive nodes However, there were two patients with involved nodes alive after four years The final tabulations at the time of the report showed that four of the patients with pneumonectomy were alive and well over six years post-operatively Among the lobectomies, there were four patients alive and well seven or more years postoperatively

* A great many surgeons have contributed significantly to progress in the surgical therapy of lung cancer Limitations of space, however, restrict this statistical summary to a few representative studies (See bibliography for other reports)

In a small selected series of asymptomatic cases derived from surveys, Overholt obtained a resectability incidence of 100 per cent, and 75 per cent showed no lymphatic spread. This yield was unusually high and contrasted with results obtained in other mass surveys. It demonstrates, however, that high resectability rates are not visionary aspirations, and helps to dispel the gloom created by resectability rates of 7 to 16 per cent (Allison), 7.5 per cent (Bjork), 4 per cent (Brooks), 4 6 per cent (Ariel), 12 5 per cent (Hollingsworth) and 7 per cent (Edwards). Unfortunately, the latter group of statistics more closely approximates the incidence of resectability among patients diagnosed in the average general hospital.

A review of Overholt's operative results between the years 1932 and 1948 showed 162 resections (27 per cent of the total cases and 56 per cent of the explored cases), with a mortality rate of 18 per cent There were ten patients who survived five years postoperatively, of whom eight had no extrapulmonary extension It is of considerable importance that two patients survived five years despite extrapulmonary invasion.

Ochsner's series includes 948 patients with 332 resections (35 per cent of the total group and 65 per cent of the cases explored). The cases were derived from the Charity Hospital, New Orleans, and the Ochsner Clinic during the period 1935–51 The mortality rate of the resected cases was 20 per cent Comparison between the private patients and the Charity Hospital patients showed the incidence of exploration to be 66 per cent in the private patients and 37 per cent in the hospital patients, the rates of resectability in the two groups were 43 per cent and 23 per cent, respectively. This tendency of private patients to avail themselves of medical care sooner than charity patients has not been generally observed. Jones, in a selected study of 633 consecutive private patients over a period of ten years, found little evidence of increased resectability on the basis of earlier and more frequent examinations

Of Ochsner's 332 resections, there were 232 (70 per cent) that were classified as palliative because of involvement of the mediastinal nodes, pleura, pericardium, chest wall, or diaphragm Although the over-all mortality rate was 20 per cent, it was only 14 per cent for the noninvasive cases The operative deaths were caused chiefly by cardiac and pulmonary complications. The five-year survival rate for the resected cases was 19 per cent and for the cases without extension of the tumor it was 38 per cent. Of the total group of 948 patients, only 6 per cent were alive at the end of five years.

Aufses analyzed the results at the Mount Sinai Hospital, New York City, between the years 1935 and 1948 There were 959 cases of which 330 (35 per cent) were explored and 165 (17 per cent) resected The follow-up showed 25 patients alive and well after four or more years, 2 not traceable after seven and ten years, respectively, and 6 dead of causes other than lung cancer The total potential salvage was 33 patients out of the original group of 959.

Rienhoff operated on 502 patients between the years of 1933 and 1949 and found 158 (31 per cent) resectable Metastatic invasion of the lymph nodes was present in 70 per cent of the resected cases There were 41 post-operative deaths (26 per cent), and 85 of the resected patients (54 per cent) were dead within one year Among the survivors, there were 16 patients alive five or more years and 5 patients alive twelve or more years.

Graham reviewed his surgical experiences of 402 pneumonectomies at the Barnes Hospital in St Louis. Whereas the post-operative mortality rate was about 50 per cent in the early years, it had declined to 8 per cent in 150 pneumonectomies in the period 1945–50 The incidence of resectability was 22 per cent between 1945 and 1947, and it had not increased much in later years This has also been the experience of many other surgeons Until there is developed greater diagnostic acumen in the detection of noninvasive cases, the resectability rate cannot be significantly improved Graham's follow-up study showed that of 53 patients operated before 1942, 15 were alive and well, giving a survival rate of 28 per cent.

Histologic Correlation Many attempts have been made to correlate the clinical course of bronchogenic carcinoma with the predominant cell type found on histologic examination However, the variations in terminology among pathologists have left this problem still unresolved The accumulation of surgical experience in pneumonectomy has led to frequent observations correlating the post-operative course and survival with the histologic type of bronchogenic carcinoma It is the opinion of most observers that patients with squamous cell tumors respond better to surgical extirpation than those with other cell types, and that the undifferentiated carcinomas respond poorly

Moersch and McDonald correlated the surgical results at the Mayo Clinic with the cellular type of the lesions resected Squamous cell carcinoma was the most frequent type occurring in 395 (39 5 per cent of all the cases) Exploratory thoracotomy was done in 245 cases (62 per cent) of the squamous cell cancers and resection in 182 (46 per cent) It is of significance that 74 per cent of the explored cases were resectable. Study of the surgical specimens revealed that practically all of the tumors were centrally located Follow-up of the resected cases showed that in 68 of the patients traced two years post-operatively, 38 (55 8 per cent) were alive, and of 27 patients traced five or more years post-operatively, 14 (51 9 per cent) were alive None of the nonresected cases was alive at the end of three years

Adenocarcinoma comprised 137 (13 7 per cent) cases of the entire series There were 84 explored cases (60 per cent) and 56 resections At the end of two years, a third of the resected patients were living and well The small cell or 'oat cell' type occurred in 90 (9 per cent) of the total series Exploration was performed in 30 cases (33 per cent) and resection in 15 (17 per cent) There were 3 survivors after two years and 1 after five years There were 378 (37 8 per cent) large cell carcinomas Exploratory thoracotomy

was done in 186 (49 per cent). In 108, resection was performed (58 per cent of the explored cases). In 44 per cent of the resected cases, the patients were alive two years post-operatively.

Brea observed 880 cases in Buenos Aires between the years 1944 and 1952 There were 311 explorations (35.3 per cent) and 200 resections (22 7 per cent of the total group and 64 3 per cent of the explored cases) During the past five years of study the incidence of resectability had almost doubled The operations included 159 pneumonectomies with 35 post-operative deaths (22 per cent) and 41 lobectomies with 2 deaths (4 8 per cent). The average operative mortality for the 200 resections was 18 5 per cent. There were 31 deaths (26 per cent) in the 119 cases requiring extensive dissection of adjacent tissues or intrapericardial maneuvers, whereas there were only 6 deaths (7 4 per cent) in the 81 cases with typical dissections.

The follow-up of 163 patients who survived resection revealed 150 traceable patients with 92 deaths within two years Among the 58 living patients there were 34 who survived two or more years, 15 who survived four or more years, and 7 who survived five or more years The percentage of two-year survivals was greater among the lobectomies than among the pneumonectomies Of 104 pneumonectomies, there were 25 survivals (24 per cent) over two years and, among the 21 lobectomies, there were 9 (42 per cent) The average post-operative two-year survival rate was 27.2 per cent

A study of the histological classification of 33 resected cases with two-year survival revealed that 20 (60 6 per cent) were cases of epidermoid carcinoma of which 18 were non-metastatic There were 17 pneumonectomies and 3 lobectomies Of the 12 (36 3 per cent) adenocarcinoma cases surviving 2 years, 11 had no metastases There were 6 pneumonectomies and 6 lobectomies in the adenocarcinoma group. These results indicate that the most important surgical prognostic factor is localization of the cancer within the confines of the lung The histologic type is important in that epidermoid carcinomas have shown the best surgical response, but histological classification is apparently secondary to localization of the tumor. This is emphasized by 12 adenocarcinoma cases with two-year survival and, particularly, by the 6 cases with lobectomy. The extent of the surgical resection did not significantly influence the survival rate, and Brae concluded that what was needed most was earlier diagnosed cases and not more extensive surgery

Surgical Therapy in England Taylor and Waterhouse summarized the results among representative surgeons in several English centers Of the 1,239 pneumonectomies analyzed, there were 313 with sufficiently detailed data for study In the period 1939–40 the operative mortality was 38 per cent, and in 1947–8 it was 20 per cent Considerable difficulty was encountered in evaluating the survival rates because of incomplete records. In the centers where detailed figures were available, the five-year survival rate was 13 7 per cent.

Of 66 pneumonectomies reported by Tudor Edwards in 1946, there were 5 cases who survived five years Brock, in 1948, reported 101 resections (86 pneumonectomies) with 8 patients who survived five years. Sellors performed 180 resections (122 pneumonectomies) with 10 patients who survived more than four years, and 5 who survived more than five years. In Mason's series of 202 pneumonectomies reported in 1948, there were also 5 patients who lived more than five years

Pre-operative Evaluation

Surgical excision of a tumor is useless if the patient cannot physiologically survive the operation Careful consideration must be given to the patient's cardiovascular and pulmonary reserve The history usually gives an important clue, and the complaints of precordial pain, ankle edema, and dyspnea on exertion must be carefully considered Clinical and electrocardiographic examinations of the heart are essential for evaluation Patients who have had myocardial infarction or who have cardiac arrythmias should have excision of the least possible amount of lung tissue, and to avoid arrythmias, the pericardium should not be entered Individuals who have long thin chests with oblique ribs have a more efficient ventilatory apparatus than those with a short thick chest with horizontal ribs Clinical auscultation should reveal that the patient can accentuate his breath sounds Patients who can move air well can move secretions well, and therefore can clear their tracheobronchial trees in the post-operative period Fluoroscopic evaluation of the costal motion coupled with the clinical auscultatory findings usually give an adequate index of the ventilatory ability of the patient Although elaborate tests of pulmonary function have been devised, they are rarely needed except in marginal cases

The decision to operate a patient with marginal reserve depends upon the amount of functioning lung tissue to be excised If a lesion demands pneumonectomy with the sacrifice of considerable functioning lung tissue, marginal reserve may contraindicate the operation On the other hand a patient with a similar reserve may withstand an operation quite satisfactorily if there is little or no functioning lung tissue in the lung to be removed On occasion lobectomy may not be the ideal operative procedure but is demanded by the patient's limited respiratory reserve The ideal cancer operation may not always be the ideal operation for such a patient Pneumonectomy with mediastinal dissection carries more risk than pneumonectomy alone

Although a carefully executed operation is tantamount for the expectation of a good result, the best operative performance is occasionally followed by complications unless meticulous attention is given to logical pre- and post-operative management The successful pulmonary resection demands that the patient be in the best possible physical condition prior to operation, and

that the post-operative *course is closely* supervised so that the patient's physiological state is as ideal as possible.

To avoid such complications as aspirational pneumonia and [illegible]

[illegible] During the aging process teeth decay and gums harbor infection that *may* be aspirated into the tracheobronchial tree Since the bacterial flora *of the mouth* and naso-pharynx also inhabit the bronchial tree, resection of the lung is *always accomplished* in the presence of bacterial contamination. Pre-operative attention to the structures of the mouth and naso-pharynx such as the teeth, tonsils, and sinuses, should be controlled prior to operation *to avoid infection* in the residual lung and the pleural cavity.

The preservation of the bronchial cleansing mechanism is important to prevent atelectasis, lung abscess, and aspirational pneumonias It is dependent upon cough, bronchial peristalsis, and the ciliary action The ciliary action is microscopically active at all times, sweeping noxious materials into major airways Bronchial peristalsis occurs during each respiratory cycle through elongation and foreshortening of the bronchus When the patient is encouraged to cough at frequent and periodic intervals bronchial and pulmonary secretions are moved into major airways so that they may be raised as sputum. Open airways not only prevent infection and atelectasis but also assure adequate ventilation and oxygenation. Paradoxical motion after chest operations must be controlled to prevent ineffective cough and deficient pulmonary ventilation. Pain control is important so that the patient can co-operate to make the cough effort effective.

Immediate and complete re-expansion of the residual lung after a lobectomy is important to prevent an empyema or an incapacitating pleurisy Complete re-expansion contributes alveolar units for gas exchange, and in the absence of pleurisy assures good diaphragmatic motion and maximum restoration of function.

Pre-operative Preparation

If the pre-operative evaluation reveals evidence of latent or manifest cardiac insufficiency, every attempt must be made to stabilize prior to surgical intervention Nutrition should be at as optimal a level as possible, and transfusions should be given to restore normal blood volume.

Prior to operation the quantity of sputum should be reduced to a minimum to avoid difficulties with oxygenation on the operating table and functional damage by the production of post-operative aspiration pneumonia. Antibiotics and postural drainage may be useful to help reduce secretions to a minimum. Patients are best prepared for an early afternoon operation rather than an early morning operation, because secretions are as a rule more often raised in the morning hours

The Operative Approach (Fig 1)

The operative approach is designed to offer the most versatile access to the cardinal hilar structures The operator should be in position to dissect the hilum anteriorly and posteriorly and to gain ready access to the intra-pericardial anatomy should it be desirable or necessary The bronchus is the key to every hilar dissection, and its early isolation and division not only controls secretions but also simplifies pulmonary resection

The postero-lateral approach offers the most varied access to the cardinal hilar structures, and produces minimal post-operative disability and deformity The advantages offered by prone position seem to be outweighed by the versatility of the postero-lateral approach The anterior incision places the cardinal hilar structures at considerable distance from the operator and only the most skillful surgeon should be placed at such a disadvantage

Residual secretions may be controlled by the position on the table or the use of the Carlens double lumen tube Secretions originating in the upper lobes adhere to the outer wall of the main bronchus if the head of the table is depressed, allowing the anesthetist to recover them with an aspirating catheter and avoid spill to other parts of the lung Lower lobe secretions are trapped by elevation of the head of the table

After the endotracheal tube has been passed and the anesthetist gives permission, the patient is carefully turned to the lateral position The under thigh and leg are flexed and a large pillow is placed between the legs A roll of foam rubber is then placed under the lower axilla to protect the nerves and vessels to the dependent upper extremity The upper extremity of the operated side is allowed to rest dependently over the side of the table, which is padded to avoid pressure damage The chest is prepared and the table draped to allow the anesthetist good visual field of the wound and diaphragm The operative region is draped in such a fashion that the tube sites for re-expansion and drainage will be easily exposed

Step I A curved postero-lateral incision is made, extending from the level of the second dorsal vertebra downward about 2 to 3 cm from the midline (Fig 1A) The incision courses forward so that it runs about 4 cm beneath the tip of the scapula and extends to the anterior axillary line This allows the scapula to fall away from the thoracotomy wound and avoids obstruction of the upper end of the wound Stockinette, instead of skin towels, is clipped to the wound, placing tension on the incision

Step II The fascia of the auscultatory triangle is divided and the latissimus dorsi and serratus anterior are tented outward and divided with one continuous sweep of the knife (Fig 1B and 1C) Packs are applied and bleeding points are secured The trapezius and rhomboids are then managed in a similar fashion

Step III The sacrospinalis muscle is then freed from its costal attachments above and below the rib to be removed, or interspace to be entered The rib

is deperiostealized and excised from the level of the transverse process forward to the mid-clavicular line. The pleural cavity is then entered at a point

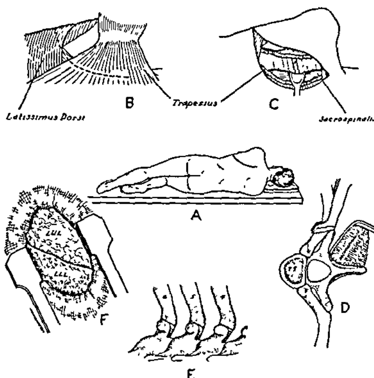


FIG. 1.

A Patient in right lateral position with incision outlined

B. Diagrammatic representation of the shoulder girdle muscles to be divided.

C After division of muscles, costal cage is exposed.

D Demonstration of oblique division of rib at level of transverse process

E Posterior view of transverse processes and ribs

F Exposure with a Finochietto Retractor.

placed away from the disease If an intercostal incision is utilized, the incision is made in the center of the interspace selected anteriorly After the incision has been enlarged to 5 cm. a retractor is inserted and turned sideways to tense the intercostal muscles so that the remainder of the incision may be made with ease in the center of the muscles. The ribs above and

below are then divided at the level of the transverse process without disturbing the periosteum to accelerate callous formation and healing in the late post-operative period (Fig 1D and 1E) The edges of the Stille laminectomy shears are placed obliquely so that the heel is at the level of the transverse process This technique gives the ribs more stability and therefore there is less pain in the post-operative period

The wound edges are protected with pads and a Finochietto retractor is inserted The pleural cavity is explored and the problem evaluated (Fig 1F)

Exploration

The ideal pulmonary resection removes the least amount of lung which is consistent with a 'cure' in order to preserve the maximum amount of pulmonary function At exploration the operator must first determine whether or not a cure is feasible Experience indicates that lobectomy is justifiable in the presence of a well-circumscribed lesion Next he must decide on the dimensions of the operation (lobectomy or pneumonectomy) to obtain a cure, and finally mediastinal dissection must be evaluated as a supplementary step in the operative procedure

A palliative resection may be decided upon if a cure is not possible Enlarged nodes are not always invaded where pulmonary suppuration has been a feature, and their presence should not deter the surgeon Frank invasion of the nodes is occasionally followed by successful resection Obvious incurability, evidenced by the presence of matted nodes, distant metastases, and pericardial invasion should be considered, as well as the severity of symptoms and the risk involved Lobectomy may also be utilized in the palliative type of operation, it has the added advantage of the preservation of pulmonary reserve

Exploration is carefully carried out taking care (1) not to massage secretions into the bronchus, or (2) to dislodge tumor cells into veins Before proceeding, resectability of the tumor invading the chest wall should be determined Mobilization may compromise the blood supply of the tumor, and may result in necrosis with bronchopleural fistula during the post-operative period

Technique of Left Pneumonectomy (Fig 2)

Step I The left standard postero-lateral incision is made and the pleural cavity explored Decision is made to perform a left pneumonectomy

Step II The lung is drawn forward and the left main bronchus palpated, remembering that the artery lies immediately cephalad and the inferior pulmonary vein caudad Three traction clamps are placed at the junction of the lung and the left main bronchus The tissue superficial to the bronchus is dissected free, clamping and dividing lymphatics, vagal branches to the lung, and bronchial arteries The boundaries of the bronchus are identified

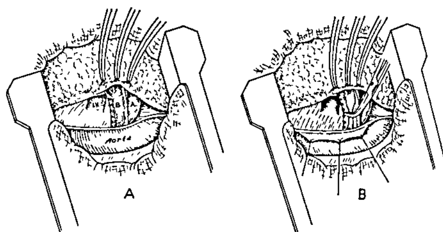
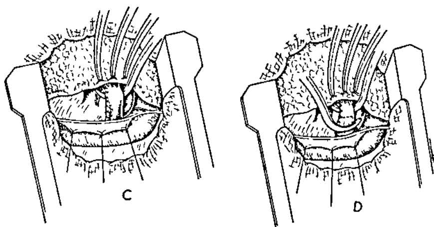


Fig 2. *Left Pneumonectomy*

A The left main bronchus (B) is palpated The pulmonary artery (A) lies immediately above and the inferior pulmonary vein (I V) below.

B The mediastinal pleura is opened, and the bronchial arteries are clamped and divided.



C The left main bronchus is surrounded, avoiding the pulmonary artery and vein

D The left main bronchus is then clamped and divided.

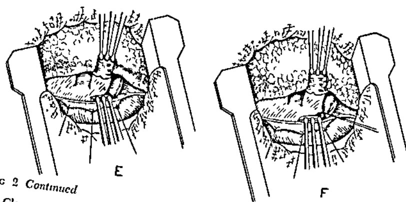
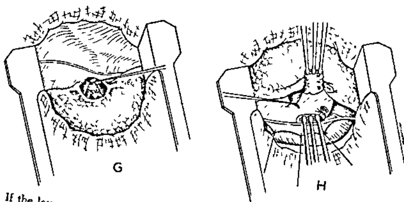


FIG 2 *Continued*

E Clamps are placed on the proximal and distal stumps of the bronchus, providing handles to retract the lung and the proximal stump

F The pulmonary artery is then isolated, ligated, and divided



If the lesion is in the upper lobe, the superior vein is secured next The lung retracted posteriorly and dissection of the superior pulmonary vein (s v) is npleted Preservation of the phrenic nerve is desirable

The lung is then retracted forward and the inferior pulmonary vein is isod, ligated, and divided

and the space between the vein and the artery is opened as close to the mediastinum as possible. Often a finger (the right index) may be passed downward and behind the left main bronchus, drawing it posteriorly and controlling the secretions, so that the lower edge may be dissected free. A large 'J'-shaped clamp is then passed around the bronchus, and it is clamped

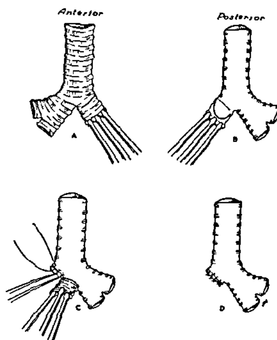


FIG 3 *Bronchial Closure* Traction on the proximal stump affords exposure for proper division and closure of the bronchus A relatively long membranous cuff is fashioned while the cartilaginous portion is divided close to the trachea (A and B) The latter incision is first carried three-quarters of the way across the bronchus, providing a handle for traction while the stump is closed flush with the trachea (C and D)

and divided. Allis clamps are placed on the proximal and distal stumps, each group being held together by elastic bands Those on the distal stump act as a handle to facilitate the remainder of the resection, and those on the proximal for ease in the performance of the mediastinal dissection where indicated

Step III The tissue overlying the pulmonary artery is tented outward and the sheath is entered. Dissection is readily carried out within this plane, and when enough length is obtained a medium right angle clamp is passed around to recover a ligature so that the vessel may be ligated Sufficient

length is obtained and the distal stump of the artery is clamped, divided, and ligated.

Step IV. After drawing the lung posteriorly and inferiorly, the superior pulmonary vein is dissected free Care is taken not to injure the phrenic nerve during the course of this dissection The vein is ligated as close to the pericardium as possible After ligation and division of the superior vein, the lung is drawn forward and the inferior pulmonary vein treated similarly. The lung is then removed. It is important that the bronchial closure be flush with the trachea so that secretions may not stagnate in a blind pit. A relatively long membranous tongue is fashioned to be apposed to a short cartilaginous cuff The incisions are made halfway through the bronchus The Allis clamps are then rotated through 45 degrees and sutures are placed and tied The remainder of the bronchial stump is then divided and is closed with sutures Care is taken to avoid traction on the closure sutures (Fig 3, Technique of Bronchial Closure)

It is not necessary to pleuralize the bronchial stump after left pneumonectomy because it is well hidden by viable structures deep in the mediastinum

Case Illustration Patient V A (Figs 4A and 4B)

DIAGNOSIS Bronchogenic carcinoma, left upper lobe

SIGNIFICANT FEATURES Left pneumonectomy with five-year survival, operation performed 7 months after onset of symptoms Present status—full time work tolerance

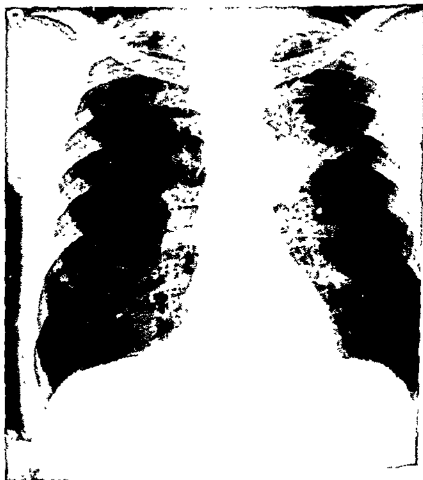
SYNOPSIS Male, aged 61, developed symptoms of an upper respiratory infection in April 1949, followed by productive cough and fever Roentgen examination in June 1949 disclosed an infiltration in the left upper lobe, which was interpreted as pneumonia Following intensive antibiotic therapy the symptoms improved and the roentgen lesion partially cleared The patient was relatively asymptomatic during the succeeding two months In October 1949, he again became ill with productive cough and fever Bronchoscopic examination and cytological studies of the sputum were negative for malignancy An exploratory thoracotomy was performed on 28 November 1949, and the left lung was removed

SURGICAL PATHOLOGY Squamous cell carcinoma originating just within the mouth of the apical segment of the left upper lobe The mass was polypoid and projected into the anterior segmental bronchus Distally each bronchus was tremendously dilated and filled with thick exudate The adjacent parenchyma showed chronic inflammatory change with multiple abscesses The lower lobe was not involved The regional lymph nodes were non-malignant On microscopic examination, the tumor showed unusual superficial noninvasive extension along the apical segment and into many of the smaller radicles

Technique of Right Pneumonectomy

Step I A standard postero-lateral incision is made and the pleural cavity explored Decision is then made as to the type of resection

Step II. The lung is retracted forward and traction clamps are applied to the posterior aspect of the lung as it joins the main bronchus The pleura overlying the right main bronchus is incised and branches of the vagus to the lung are divided The bronchial arteries are clamped and divided The bronchus is cleaned along its lateral margin proximally, and is isolated by the use of a large right angle clamp The bronchus is then clamped and divided distal to the clamp, secretions being aspirated as they appear. The right angle clamp is next removed and is replaced by Allis clamps which are held together with an elastic band

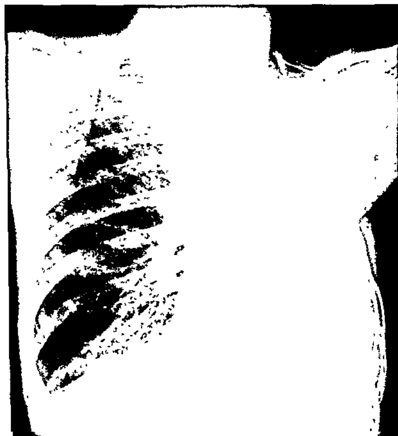


Case Illustration Patient V A

FIG 4A Male, aged 61, with history of recurrent pneumonia of five months' duration, pre-operative film shows a dense mass at the left hilar region with linear infiltrations extending into the left upper lobe.

Step III. The pulmonary artery sheath is then entered by tenting the tissue outward, incising proximally and distally On occasion it may be more convenient to ligate and divide branches to the upper lobe prior to ligating the main vessel in order to obtain adequate length distal to the point of ligation A right angle clamp is then passed behind the main artery in the periadventitial layer, so that a #0 cotton ligature may be drawn around the vessel, which is then ligated and divided, leaving as long a cuff as possible

Step IV The inferior pulmonary vein is exposed and is then ligated and divided in a similar fashion Care should be taken not to include in the liga-



Case Illustration Patient V A

Fig 4B Status post-left pneumonectomy The homogeneous density on the left side represents retraction of the hemi-thorax deviation of the mediastinum, and post-operative pleural reaction

ture the pericardial reflexion on the vein, because its elastic tissue and the constant cardiac motion may roll the tie off the stump.

Step V: Attention is next directed to the superior pulmonary vein, which is readily approached by displacing the lung posteriorly. The vein is then isolated, ligated, and divided. All that remains before removing the lung is ligation and division of the inferior pulmonary ligament.

Step VI: The bronchus is closed in similar fashion to that of the left side. Pleuralization of the bronchial stump seems to be an important maneuver on the right side. Usually it is conveniently performed using the azygos vein and its pleura Occasionally the superior tributary of the azygos vein requires ligation and division for adequate mobilization It may be necessary to utilize a free graft, or opened free graft, of the azygos vein Pedicle grafts of intercostal muscles have been used by Brock with considerable success. Crafoord excises the cartilages and produces a two-layer closure, a method which has been very effective in his hands. Brewer has described a pleuropericardial fat pad graft The actual method of closure seems to be of little importance provided that a crypt is not left in the bronchial stump for the stagnation of secretions, and that the closure is covered with viable tissue

Mediastinal Dissection

The addition of a mediastinal dissection seems to be a logical development in the evolution of surgery for pulmonary neoplasms. It must be emphasized at the outset, however, that the anatomical complexities of the 'main street' of the chest do not allow the desirable usual *en bloc* maneuvers The esophagus and aorta cannot be removed even in part, nor can the opposite bronchus and vertebral bodies, nor can a significant segment of the trachea What can be removed is limited to tissues contiguous to these essential structures, such as mediastinal pleura, underlying fat, regional lymph nodes, and pericardium. The pulmonary veins may be excised *in toto* and even a portion of the auricular wall, but these are palliative procedures.

Mediastinal dissection is designed solely to excise all possible regional nodes and lymphatics The procedure should be considered an adjunct to the primary operation of excision of a lobe or lung. It should be accomplished, therefore, after the primary operation has been completed.

The advocates of mediastinal dissection have uniformly reported an increase in morbidity following its application with pulmonary resection The usual complications are cardiac arrythmias, but some have mentioned mediastinal shift and bronchial fistula as problems during the post-operative period Serious cardiac arrythmias may be held to a minimum by proper selection of patients and the early use of cardiac drugs, such as digitalis, quinidine, or pronestyl Mediastinal shift may be controlled by proper post-operative care Bronchial fistula almost never occurs if the bronchus is closed at the tracheobronchial junction. On the right side the bronchial stump is

covered with viable tissue, whereas on the left the bronchial closure is hidden and occluded by the adjacent mediastinal structures high in the aortic window

Because metastases from lung carcinoma occur by lymphatics, pulmonary veins, and by direct extension, the bronchus is divided first, thus interrupting the bronchial artery supply to the lung and the major peribronchial lymphatic channels If the pulmonary vein is ligated first, the peribronchial lymphatic flow is increased 25-fold Furthermore, the lung becomes a cumbersome structure, turgid with blood due to the systemic pressure in the bronchial arteries, which drain mainly into the pulmonary veins Probably an insignificant amount of blood is delivered through the pulmonary artery after the chest has been opened The major flow is via the bronchial arteries under the systemic pressure The surgeon must make a compromise and divide first the structure which will make the operation least difficult, safest for the patient, and give the least risk of spreading tumor cells during the course of the operative procedure The remainder of the hilar dissection may then be carried out quickly with relative ease and with a minimum of manipulation. The pulmonary artery is immediately available for ligature, followed by ligation of the pulmonary vein draining the involved lobe After the lung has been removed a systematic clean mediastinal dissection may be performed, excising mediastinal pleura, fat, and lymphatics including the supra-aortic, periesophageal, pericardial and subcarinal components A more complete mediastinal dissection can be performed after completion of the pulmonary resection Furthermore, it is carried out when it is known that a possibly curative resection has been accomplished, and that the patient will tolerate further surgery

Right Upper Lobectomy (Fig 5)

Examination of the pathologic process has convinced the operator that lobectomy will be as radical as a pneumonectomy, and will preserve the function of the middle and lower lobes

Step I. The pleura over the right upper lobe bronchus is incised, exposing the bronchial arteries and the pulmonary branches of the vagus nerves which are clamped and divided (A) Traction clamps are placed on the lung tissue at the junction of the lung with the posterior aspect of the right upper lobe bronchus The peribronchial tissue is then released by sharp and blunt dissection The bronchus is then easily circumscribed by the meticulous use of oblique and right angle clamps, with reasonable security in so far as the artery and veins are concerned, which occupy an antero-superior and antero-inferior position respectively As the angle between the right upper lobe bronchus and the intermediate bronchus is developed the lymph node and posterior ascending artery should be avoided Once the bronchus is isolated, it is doubly clamped and divided between the clamps (B)

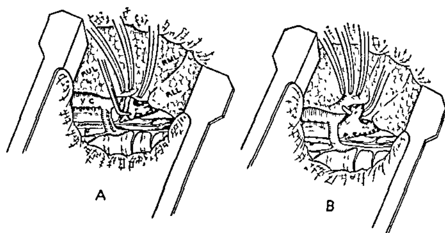
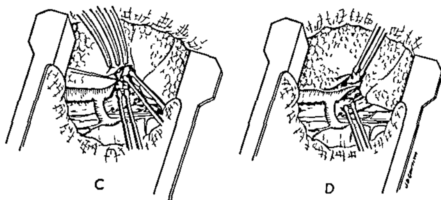


Fig 5 *Right Upper Lobectomy*

A The mediastinal pleura is incised and clamps are applied to the lung at its junction with the right upper lobe bronchus. The bronchial arteries and vagal branches are clamped and divided.

B The right upper lobe bronchus is then surrounded and divided, taking care to avoid the branches of the pulmonary artery and vein



C Clamps on the proximal and distal stumps act as retractors The branches of the pulmonary artery are then isolated, ligated, and divided

D. After division of the branches to the right upper lobe, the descending pulmonary artery is visualized anterior to the bronchus

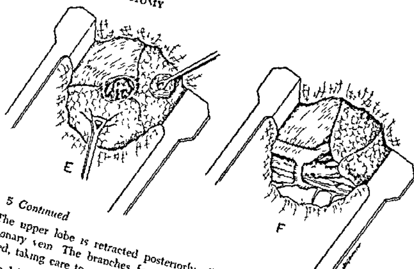


Fig 5 Continued

E The upper lobe is retracted posteriorly allowing dissection of the superior pulmonary vein The branches from the upper lobe are isolated, ligated and divided, taking care to preserve the branch from the middle lobe

F The lobe is then removed and the bronchus is closed after re-amputation close to the main bronchus

Step II Attention is then directed to the branches of the pulmonary artery which enters the upper lobe from the antero-superior aspect (C) Care should be taken to enter the proper plane The sheath which surrounds the vessel is entered by sharp dissection, and the vessel defined in a proximal and distal direction continuing the dissection into the lobe (D)

Step III The lobe is then retracted posteriorly and the superior pulmonary vein isolated (E), avoiding the phrenic nerve and bearing in mind that the vein to the middle lobe must be identified and preserved Isolation and ligation technique, similar to that used with the pulmonary artery, is employed, respecting the proximity of the descending pulmonary artery behind

Step IV Removal of the lobe may then be readily carried out (F) In 30 per cent of the cases an incomplete fissure is present, requiring traction dissection technique as used in segmental resection

Step V The bronchus is then re-amputated very close to the main bronchus, and is closed with end-on sutures of #000 silk The wound is next carefully irrigated with saline Pleuralization of the bronchial stump is usually carried out, using viable tissue by free or pedicle graft

Left Upper Lobectomy

Control of the bronchus to the upper lobe is not convenient until the branches of the pulmonary artery concealing it are skeletonized, ligated, and divided A complete fissure between the upper and lower lobes facili-

tates the dissection and encourages the operator to perform a lobectomy for a peripheral well-circumscribed lesion.

Step I The pleura over the pulmonary artery is incised and the proper plane entered for easy identification of the pulmonary artery and its branches Frequently there are lymph nodes present that should be dissected in such a fashion that they will be removed with the upper lobe. Occasionally small inter-lobar veins will be encountered which must be clamped and ligated to avoid troublesome bleeding. There are usually five branches of the artery to the upper lobe. Dissection proceeds outward within the sheath of the vessel, utilizing proper clamps and forceps to tent the encompassing tissue away from the vessel When the small gauze dissector is used care must be taken to avoid stroking toward the main vessel Stroking should always be directed toward the periphery to avoid splitting the main artery in the delicate crotch at the site of the bifurcation The branches are meticulously isolated, ligated, and divided.

Step II The bronchus is then readily palpated and the peribronchial tissue is released, care being taken to ligate the branches of the bronchial arteries. A right angle clamp is carefully passed around the bronchus with reasonable impunity The bronchus is then clamped and divided, grasping the distal stump with Allis clamps, which are then held together as a unit by an elastic band. The right angle clamp on the proximal stump is then replaced in a like manner with Allis clamps

Step III The lobe is then displaced backward, and the interval between the phrenic nerve and the pulmonary veins is developed The pulmonary vein and its branches are then identified, isolated, ligated, and divided The lobe's cardinal structures have now been divided Only a few strands of lymphatic tissue remain which should be ligated and divided

Step IV Mediastinal dissection is possible after a lobectomy by removing all tissue around the pulmonary artery and main bronchus

The lower lobe is retracted forward, and the main bronchus is elevated by traction on the Allis clamps previously used to occlude the upper lobe bronchus. The peribronchial tissue attached to the left main bronchus is then removed from the level of the left upper lobe bronchus, including all of the subcarinal nodes, extending the dissection down the opposite bronchus to the level of the right middle lobe. The adjacent periesophageal nodes are then excised The pulmonary artery is skeletonized next, excising the adjacent nodes that lie in the aortic window and adjacent to the superior pulmonary vein The main bronchus is retracted posteriorly, and the tissue surrounding the vein and the anterior aspect of the main bronchus is excised.

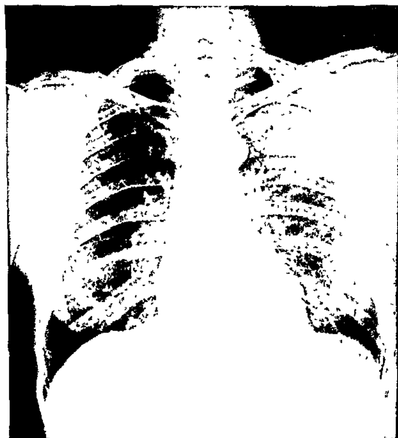
A supra-aortic dissection may be carried out, dissecting out all of the pleura and underlying fat and nodes from the mediastinum Care should be taken to preserve, if possible, the phrenic and recurrent laryngeal nerves

Step V The bronchus is then re-amputated and closed as described under right upper lobectomy (p 247)

(p 247)

CASE ILLUSTRATION PATIENT C B (Figs. 6A and 6B)

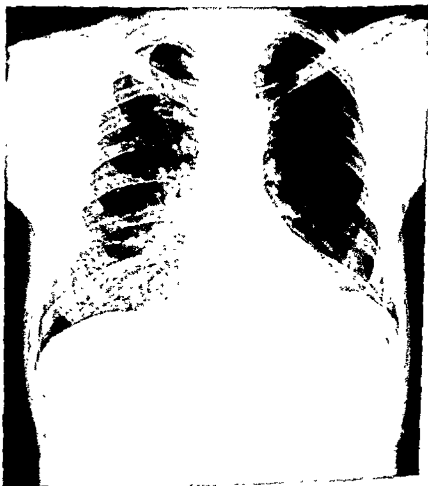
DIAGNOSIS Bronchogenic carcinoma, left upper lobe
SIGNIFICANT FEATURES Left upper lobectomy with mediastinal dissection, three-year survival Present status—full time work tolerance



Case Illustration Patient C B

FIG 6A. There is a homogeneous ovoid density occupying the major portion of the left upper lobe The left hilar shadow is slightly enlarged The left lower lobe and the right lung are negative

SYNOPSIS: Male, 64 years of age, with history of recurrent small hemoptyses of one month's duration Serial roentgen examinations for three months prior to onset of symptoms revealed an expanding homogeneous density in the left upper lobe. A thoracotomy was performed on 21 December 1951, four months after the initial X ray had revealed the presence of the left upper lobe shadow At operation, the tumor mass was found in the left upper lobe adherent to the chest wall, necessitating extra-pleural dissection The lesion appeared confined to the lobe of origin, and a lobectomy was done with mediastinal dissection



Case Illustration, Patient C B

FIG. 6B *Status:* four months post left upper lobectomy The lower lobe now occupies the major portion of the left hemi-thorax and is enveloped apically and laterally by a mantle of pneumothorax The mediastinum is slightly shifted to the left and the left diaphragm is elevated.

SURGICAL PATHOLOGY. The tumor was circumscribed, hard, yellowish-white and measured 6 cm in diameter It occupied the apex of the lobe and extended to the pleura Branches of the apical bronchus showed varying degrees of occlusion by the tumor The distal bronchi were dilated The lymph nodes between the left upper and lower lobes contained nests of malignant cells, all the other nodes were negative Microscopic examination showed the tumor to be a non-keratinizing squamous cell carcinoma

Right lower lobectomy may be indicated for a well-circumscribed tumor, especially if the upper lobe is relatively large Because of the arrangement of the bronchi and lymph nodes, resection of the middle lobe is often also required The operator usually commences the dissection in the long fissure with ligation and division of the descending pulmonary artery The intermediate bronchus is then surrounded, clamped, and divided. If the fissure is closed and the dissection is difficult due to inflammatory change, the bronchus may be dissected first by approaching it posteriorly distal to the upper lobe bronchus The veins are ligated and divided, care being taken to preserve the upper lobe veins The subcarinal lymph nodes may then be excised, using the proximal bronchial clamp as a handle to facilitate the [illegible] dissection

Left lower lobectomy for carcinoma is an operation designed [illegible] for well-circumscribed tumors of the basal segments The dissection [illegible] mences with skeletonization of the descending pulmonary artery [illegible] fissure, in such a fashion that all the overlying lymph nodes are [illegible] with the lower lobe Great care is taken to preserve the [illegible] pulmonary artery to the upper lobe The lower lobe bronchus is [illegible] clamped, and divided The inferior pulmonary vein is next [illegible] divided. The subcarinal lymph nodes are then excised

Wound Closure for Lobectomy

Two tubes are placed for drainage and re-expansion of the [illegible] The upper tube (an F-24 red rubber catheter) is fenestrated [illegible] 3 cm. and is passed through the anterior axillary line, beneath [illegible] major and minor muscles, to enter the pleural cavity through the [illegible] interspace The tube is then sutured to the pleura of the [illegible] lower tube (an F-26 catheter) is similarly fenestrated and [illegible] the antero-lateral chest wall obliquely, so that the tip lies [illegible] the level of the dome of the diaphragm on expiration

Both tubes are joined by a glass 'Y connector to a pleural [illegible] suction is regulated by a water manometer All clotted [illegible] from the pleural cavity and 300 to 500 cc of saline is [illegible] The saline acts as a diluent to blood that accumulates in the [illegible] of the pleural cavity and avoids clot formation which [illegible] tubes After closure of the wound oozing is reduced by [illegible] lung

The *intercostal* wound is then apposed with a *Bailey* approximator and is closed with interrupted sutures, taking care to replace the divided ribs in their proper position. The *serratus anterior* is repaired anatomically, followed by re-suture of the latissimus dorsi The rhomboids and trapezius are then closed in layers. The *subcutaneous* layer and skin are repaired with interrupted sutures.

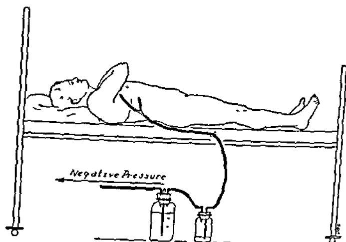


FIG 7. *Pleural Drainage.* The patient should lie on his operated side or back The drainage tubes are arranged so that there will be gravity flow to the pleural drainage bottle. A simple water manometer regulates the negative pressure from 20 to 25 cm. of water.

Post-operative Care

The most important feature of the post-operative care of patients who have had pulmonary resection is the maintenance of a good airway. Cough must be encouraged at regular and frequent intervals so that secretions may be raised to prevent obstruction of the lobar and segmental bronchi The patient is given assistance by manual pressure over the rib fracture sites posteriorly to minimize painful motion, and anterior counter pressure to aid in fixing the chest

Nasotracheal suction is utilized to induce cough and aspirate secretions when simple cough efforts fail. The nasal passages may be anesthetized with a short-acting topical anesthetic A moderate size catheter is advanced to the region of the pharynx and is suddenly advanced through the open glottis during deep respiration or immediately after cough Should prolonged suction be necessary the catheter is left in place within the proximal trachea while oxygen is delivered through it intermittently

Bronchoscopy is occasionally necessary and can be accomplished in bed Only the oropharynx is anesthetized, so that there will not be diminution of the cough reflex The patient's bed is racked to the high Fowler's position

with the operator standing on the frame behind the patient. Oxygen is c livered through the bronchoscope after it has been passed into the trache

Tracheotomy is occasionally required to aid in the recovery of tracheo bronchial secretions. In a small number of patients with marginal reserve it may be advisable to carry out this procedure at the completion of the pulmonary resection. It also gives the advantage of reduction of dead space and decreasing expiratory resistance. Tracheotomy may be performed in the patient's room. After induction with an intravenous barbiturate, the oxygen-carrying bronchoscope is introduced, insuring a good airway and adequate supply of oxygen. Tracheotomy is then carried out in a routine manner.

Drugs may also be useful in the management of tenacious secretions and bronchospasm during the post-operative period. Sodium iodide, intravenously and by mouth, has occasionally proved effective. Nebulized detergents have seemed very useful. Patients with bronchospasm often respond well to intravenous aminophyllin, followed by tracheal aspiration. The asthmatic patients have been best controlled by slowly administered intravenous ACTH.

Pain relief is important to relieve suffering and to insure patient co-operation during the cough effort. Demerol seems to be the most reliable agent at the present time. Several methods of long-lasting pain control have been tried, but one or more serious side-effects have discouraged their routine use.

Oxygen is administered post-operatively as long as necessary. The preferred route is by nasal catheter. This gives a high concentration of oxygen very quickly, facilitates frequent observation of the patient, and reduces the time and effort of nursing care. The oxygen should be turned off when the patient eats or drinks to avoid blasting foreign material into the trachea.

After pneumonectomy the patient is best placed in the semi-upright posi- ion lying on the back, or tilted toward the operated side. This influences entilation, gas exchange, and closure of the pleural space. Patients should ot be allowed to lie on the non-operated side, because of mediastinal shift th reduction in pulmonary reserve.

Blood volume is maintained during and after operation by blood replace- t, avoiding overloading of the vascular system by excessive fluid and rolytes. Occasionally an operation is carried out in the presence of unrecognized supra-renal gland metastases. These patients often develop serious shock states, which are best controlled by immediate cautious administration of Levophed, followed by administration of cortisone.

Gastro-intestinal distention may become a troublesome complication in the short heavy-set male during the early post-operative period. The abdominal distention is detrimental because it compromises ventilation by upward pressure on the diaphragm. Prompt gastric decompression by Levine or Devine tube with adequate pain relief will correct this complication.

The proper management of the pleural space after pulmonary resection is

as important as the operation itself. To prevent abnormal changes in the intrapleural pressure after pneumonectomy, and to insure return blood flow to the heart, the mediastinum must be maintained in the midline. A small tube is left in the chest through the anterior axillary line, entering the pleural cavity through the first anterior interspace When the chest is airtight the anesthetist is requested to make positive pressure and the tube is clamped The tube is opened when the patient is turned on his back, so that some of the trapped air may escape as the mediastinum moves back toward the midline The tube is then opened hourly 5 to 6 times at the end of expiration during the first 12 to 18 hours to allow escape of air which is displaced by accumulating fluid This is a simpler method than the use of the pneumothorax apparatus The tube can usually be removed after 48 hours because the speed of fluid formation is so slow

After lobectomy complete and immediate re-expansion of the residual lung is of great importance to restore its function, prevent oozing, occlude small alveolar leaks, and to prevent empyema Active suction of 15 to 25 cm. of water pressure is always used, regulated by a simple water manometer. Both chest catheters are connected by a glass 'Y' tube to a gravity flow tube attached to water seal to maintain constant drainage, avoiding loops in the system which will require more negative pressure than is available. The chest catheter should be milked frequently to avoid occlusion by clots As the level rises in the drainage bottle, fluid is poured off, maintaining the water seal just below the surface.

Palliative Surgery

The palliative treatment of lung carcinoma is an important aspect of the surgeon's responsibility Incurable patients may benefit by palliative resections because of complications such as infection, obstructive emphysema, or hemorrhage To justify this approach the mortality rate must be minimal, and the chance of respiratory insufficiency small.

Secondary pulmonary suppuration may be controlled by modern antibiotic therapy, but eventually may become refractory to treatment Resection under these circumstances may prolong life and relieve the toxic symptoms Uncontrolled recurrent hemorrhages caused by necrosis may become extremely distressing to the patient Usually the situation is very grave when this occurs, but the subsequent survival time cannot be predicted

At the time of thoracotomy the surgeon may be confronted with mediastinal metastases and a lesion which may be resected by lobectomy or seg- [illegible]

e

[illegible] patient with marginal function may present a definite problem [illegible] the tive surgical management of lung cancer. Pre-operative evaluation of the cardiovascular and pulmonary function may have indicated that only a

lobectomy was possible If during surgical exploration it is obvious that pneumonectomy is necessary to excise the tumor, closure without resection is recommended Little is accomplished if the patient is left a respiratory cripple

Practically all incurable lung cancers can be resected, but the surgical exercise is futile if it only serves to prolong suffering Palliative surgery should be constructive and should have for its objective the relief of specific distressing syndromes, particularly those caused by tissue necrosis and pulmonary suppuration

Summary

The technical advances in the surgical treatment of lung cancer have exceeded the ability to diagnose resectable cases Resectional surgery, in general, may be performed with a mortality rate as low as that for major abdominal surgery Small lesions may be resected with a negligible mortality rate The roentgen examination provides a direct approach to the detection of pulmonary abnormalities, but its limitations in differential diagnosis have been well recognized A similar situation prevails with respect to the bronchoscopic examination In many instances the diagnosis of lung cancer can be established only by exploratory thoracotomy It is important, however, that it be utilized at a time when it is of maximum benefit to the patient and should not be offered only after a period of 'watchful waiting'

Palliative surgery has a definite place in the management of lung cancer However, the surgeon should evaluate each patient as an individual problem and make his decision to explore or resect on the basis of reasonable expected improvement It is also to be considered that in cases where definitive resection is impractical, radiation therapy may be of distinct benefit in properly selected cases

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XI

Bronchial Adenoma

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Bronchial Adenoma

Adenoma of the bronchus is the most provocative of all bronchial neoplasms, and has been the subject of considerable controversy regarding pathological classification and clinical management Its features offer many interesting contrasts to bronchogenic carcinoma while resembling it clinically and radiographically

Historical Considerations Necropsy examination contributed practically all the knowledge on adenoma of the bronchus up to twenty-five years ago The first observation of a polypoid mass arising from the wall of a bronchus was made by Laennec in the early nineteenth century and recorded in his famous treatise In 1877 Heschl reported a bronchial adenoma of cylindroma type, and in 1882 Mueller described a tumor that would now be classified as a carcinoid In succeeding decades there were reports by Chiari in 1883, Horn in 1907, Kregliner in 1913, and Malkwitz in 1922, all of which further contributed to the establishment of the pathologic criteria The utilization of the bronchoscope as a diagnostic aid opened up a new era of investigation Early reports by Jackson in 1917 and Orton in 1924 paved the way for the later studies of Kramer in 1930, and Wessler and Rabin in 1932, which established bronchial adenoma as a definite clinical entity

Incidence

Bronchial adenoma comprises less than 5 per cent of all bronchial neoplasms, and thus far *not* more than a thousand cases have been recorded The majority of the cases were reported within recent years According to Foster-Carter, the total number of cases prior to 1941 did not exceed a hundred This rapid increase in the incidence of adenoma parallels that of

bronchogenic carcinoma during the same era, and is a reflection of the increasing experience in the diagnosis of thoracic disease.

In contrast to bronchogenic carcinoma, the tumor is found in younger age groups The onset of symptoms usually occurs before the age of forty. Most patients are diagnosed in the third and fourth decades but the disease has also been observed in children and in elderly persons. The sex distribution also differs from carcinoma in that about 60 per cent of the cases are found in females Approximately 10 per cent of the adenomas metastasize to either *the regional lymph nodes or to distant organs.*

It is of considerable interest that so many of the patients with bronchial adenoma had been previously treated as cases of pulmonary tuberculosis. The sex and age distribution of adenoma, the chronicity of the disease, and the similarity of symptoms with tuberculosis made the latter diagnosis inevitable until the advent of better diagnostic techniques. Case histories with treatment for tuberculosis up to ten years are not unusual. Differentiation of adenoma from other pulmonary disorders such as lung abscess, recurrent pneumonia, and empyema will undoubtedly add to the incidence in future years

PATHOLOGY

Histogenesis. Adenoma of the bronchus arises from the sero-mucous glands within its wall It does not originate from the surface epithelium. The exact site of origin within the gland is unknown, since no tumor has ever been observed at such an early phase. All elements may be involved, from the epithelium of the duct to the secreting elements. A short summary of the normal histology will help clarify the pathological changes seen in adenoma

The sero-mucous bronchial glands may lie entirely within the mucosa but frequently lie in part beyond the cartilages, communicating with the mucosa through the intervening fibrous tissue. The duct is lined by a basal cell layer whose components are small, dark, and homogeneous and whose nuclei are round and central The glandular cells are relatively tall and face the lumen The mucous cells predominate and have a finely granular, sometimes vacuolated, cytoplasm which stains a pale blue The nuclei are basal. The serous cells have a darker cytoplasm and centrally placed nuclei. A few eosinophilic cells called onkocytes are sometimes present The stroma is very delicate and carries the fine vascular ramifications of the gland As is true of any neoplasm arising from a gland whose components have differing capabilities, adenoma may present a variable picture commensurate with the degree of anaplasia and the character of the cells affected.

Graham and Womack have advocated the view that the adenoma is a mixed tumor of embryonal origin. Their interpretation is based on the frequency of bony elements within the tumor Bronchial cartilages, however, frequently display osseous metaplasia, both in the presence of inflammation and as an aging phenomenon, either being an adequate explanation of its

presence in adenoma The presence of fetal lung parenchyma, suggested by them, has not been generally confirmed by other observers Origin from the

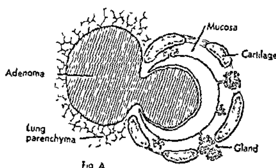


FIG 1 *Bronchial Adenoma* The polypoid mass partially obstructs the lumen of the left main bronchus and does not extend beyond the cartilages The adjacent lung is carnified due to prolonged infection distal to the tumor

onkocyte, advanced as a possibility by Stout, has been seriously questioned by others

Morbid Anatomy Bronchial adenomas usually arise in the hilar region from the main or lobar bronchi They have also been reported as arising from segmental or peripheral bronchi The macroscopic appearance is that

of a polypoid mass causing obstruction and deformity of the lumen (Fig. 1). The surface is usually smooth and has an intact mucosa, but may be eroded and hemorrhagic. The consistence of the tumor is firm and the base may be narrow or broad The mass is often shaped like a dumbbell or iceberg, with the basal portion extending into the wall through the fibrous tissue



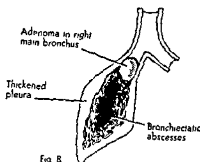


FIG 2. *The Bronchopulmonary Sequelae of Bronchial Adenoma*

A Dumbbell protrusion into bronchial lumen and lung parenchyma

B. *Obstruction and secondary infection.*

lying between the bronchial cartilages (Fig 2). The deeper portion may be much larger than the visible intrabronchial part, and project into the adjacent pulmonary tissue On section the surface is homogeneous and pale gray or white Cystic areas may be present.

Histology and Classification. The histological features of adenoma establish the basis of the classification The adenoma lies within the mucosa and is covered by an intact surface epithelium separated by a thin band of vascular connective tissue The surface epithelium may be normal respiratory in type or may show squamous metaplasia Ulceration may occur in the presence of infection Adenomas have been divided into two types· (1) carcinoid and (2) cylindroma Other classifications have been advanced divid-

ing the adenomas into three to five groups, depending on the most prominent cell type seen in the microscopic preparation In the literature, the term 'adenoma' has been used with different connotations According to some investigators it should be used to denote only the carcinoid type, and the term 'cylindroma' to denote the second type This concept is based partly on the microscopic features and partly on the clinical course of illness



FIG 3. *Bronchial Adenoma, Carcinoid Type* The tumor mass is characterized by groups of small cuboidal cells of very homogeneous appearance The nuclei are round, central, evenly stained, and free of mitoses or macronuclei The cell nests are separated by scanty connective tissue (×135)

Carcinoid In this group, the resemblance to the common basal cell carcinoma of the skin, or to the carcinoid tumor of the intestine, is very evident and the term 'carcinoid' has been generally used since Hamperl introduced it in 1937 Carcinoid is characterized by groups of small round homogeneous cells separated by scanty thin stroma containing blood vessels (Fig 3) The basement membrane is intact The nuclei are small, round, or oval, homogeneous in size and staining, centrally located, and rarely show mitotic figures The cells differ from the carcinoid of the intestine in the absence of argentophilia Occasionally gland-like spaces are present which may contain mucus

Cylindroma. Adenomas of this type have been compared to the mixed tumors of the salivary glands, and frequently closely resemble the basal cell carcinoma of the skin designated as epithelioma adenoides cysticum They differ from the carcinoids in the presence of more abundant hyaline septa,

frequently of myxomatous appearance, separating columns of cells which are somewhat larger and show a greater tendency to mucoid secretion and gland formation.

Metastasizability The feature common to both carcinoids and cylindromas is expansile growth. During the local increase in size, they may involve the adjacent lymph nodes by direct extension. This invasion is not considered true metastasis The carcinoid adenomas, which comprise approximately 90 per cent of the entire group, give rise less frequently to local lymphatic or widespread visceral metastases The cylindromatous adenomas have a much greater potentiality to metastasize. Reid classifies them as true carcinomas and suggests that the more correct term would be 'adenoid cystic carcinoma' rather than cylindroma.

A review of the literature through 1952 by McBurney revealed a total of 87 cases of bronchial adenoma with metastasis Regional node metastasis was the only evidence of extension in 46 of the 87 cases. The other 41 cases showed invasion of the following organs, in decreasing order of frequency: (1) liver, (2) contralateral lung, (3) ipsilateral lung, (4) pleura, (5) esophagus and other mediastinal structures, and (6) brain, kidney, adrenal, and miscellaneous organs Pleomorphism, mitotic figures, and irregularity of cellular pattern have been found more frequently in adenomas with distant metastases, but these features have been absent in many of the metastasizing tumors

Clinical Manifestations

The symptoms of bronchial adenoma are due to (1) the intrabronchial tumor mass and (2) infection distal to the tumor. On occasion, an extrapulmonary metastatic focus may become apparent by causing pain Because of the slow growth of the process, the clinical duration of the symptoms may persist for many years before diagnosis In many instances the over-all duration of symptoms was as long as thirty years without demonstrable distant metastases Many cases have been reported without any symptoms whatsoever

Symptoms caused by the tumor include cough, hemoptysis, wheezing, and dyspnea The tumor mass may act as a foreign body within the lumen of the bronchus and produce an irritative cough, which may be either unproductive or associated with mucoid expectoration *Pulmonary hemorrhage* is due to local ulceration or pressure necrosis by the tumor. The bleeding may be slight and manifested by blood-streaked sputum, or profuse, with frank hemoptysis of several ounces daily Hemoptysis is a very common occurrence in adenoma and often dominates the clinical picture It may recur periodically in both sexes and has been particularly noted in women at the time of menstruation Massive pulmonary hemorrhages are not unusual

Partial obstruction of the involved bronchus produces wheezing, and this is often an early symptom When the tumor completely occludes the bron-

chial lumen the wheeze disappears In cases with pedunculated adenomas, wheezing may be an inconstant symptom Dyspnea occurs not infrequently and is caused by diminished aeration of the involved lobe or lobes Attacks of paroxysmal dyspnea resembling asthma are not unusual

Bronchial obstruction eventually results in broncho-pulmonary suppuration distal to the tumor. Productive cough, fever, and recurrent episodes of pneumonitis may all be prominent features of the syndrome Large amounts of sputum and foul expectoration may result from bronchiectatic changes and abscess formation Pleurisy and empyema may occur secondary to pulmonary infection Not infrequently, patients give a history of chills, fever, malaise, and chest pain with long intervening periods of remission These manifestations are due to recurrent infections distal to the adenoma, and their significance is often obscured because of the short duration of the attacks

The general condition of patients with adenoma is usually unaffected unless broncho-pulmonary suppuration is fairly extensive Because of the slow growth of the tumor and its low incidence of metastases, there are rarely any extrapulmonary manifestations Clubbing of the digits, however, may occur in association with pulmonary suppuration In the early stages of development of the adenoma, physical examination of the chest is usually negative As the tumor enlarges, it produces physical signs because of its presence within the bronchial lumen, and the resulting infection distally

Partial bronchial obstruction of a main bronchus produces a rhonchus over the involved area Depending on the size of the growth, the rhonchus may be heard either during both phases of respiration, or only upon expiration Diminution of breath sounds and hyper-resonance are found often over areas distal to the tumor As the tumor enlarges, complete occlusion of the bronchus occurs, producing atelectasis of the associated pulmonary parenchyma with dullness on percussion, diminished tactile fremitus, and absent breath sounds Lobar or segmental infection distal to the adenoma produces dullness, crepitant rales, and altered breath sounds Recurrent episodes of pneumonitis in the same broncho-pulmonary segment or lobe should excite suspicion of bronchial obstruction

Case Illustration No 1, Patient J J (Figs 4a and 4b)

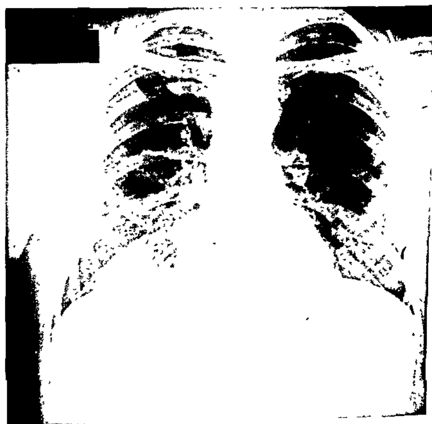
DIAGNOSIS Bronchial adenoma

SIGNIFICANT FEATURES Recurrent episodes of pneumonia, unrecognized diagnostic findings on repeated roentgen examinations, seven-year follow-up following resection

SYNOPSIS Male, age 47, hospitalized in August 1947 with diagnosis of right lower lobe pneumonia History revealed two similar episodes of pneumonia occurring in 1945 and 1946 respectively Physical examination disclosed a wheeze over the right lower lobe, posteriorly, and signs of pneumonic consolidation of the right lower lobe The roentgen examination showed a homogeneous

density involving the basal portion of the right lower lobe (Fig. 4A). Above this, at the cardiac border was a small rounded density The previous history of recurrent pneumonia suggested an endobronchial lesion, and bronchoscopic examination disclosed a polypoid mass partially obstructing the right lower lobe bronchus in the vicinity directly below the orifice of the superior segment The bronchoscopic biopsy was positive for adenoma. Resection of the tumor and the lower lobe was followed by an uneventful convalescence, and full work tolerance in three months Patient has been under observation for seven years and has had no symptoms of recurrence (Fig 4B)

SURGICAL PATHOLOGY The tumor arose from the right lower lobe bronchus directly below the orifice of the superior segment The orifice of the right lower lobe bronchus was almost completely occluded by the tumor, which did not extend beyond the level of the cartilage The lung parenchyma distal to the adenoma was the site of multiple abscesses.

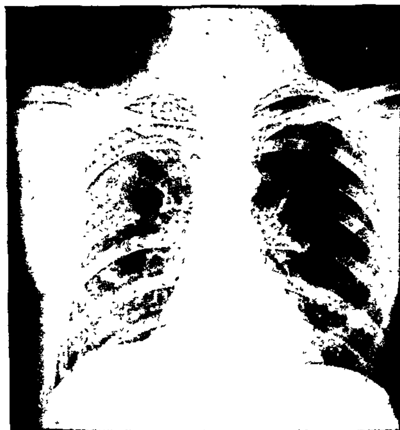


Case Illustration No 1. Patient J J

FIG 4A There is a small rounded density at the right cardiac border, level of ninth posterior rib, representing the adenoma. Below this is a larger homogeneous shadow due to pneumonic consolidation distal to the tumor.

Roentgen Findings

There is no roentgen shadow pathognostic of bronchial adenoma. There are, however, several signs indicative of partial or complete bronchial occlusion Among these are hyperventilation due to obstructive emphysema, homogeneous lobar densities due to atelectasis, and patchy densities due to localized areas of infection Varying degrees of emphysema and atelectasis may be present in the same lung when the tumor occludes more than one bronchus Bronchial adenoma may also present itself, radiographically, as a circumscribed density adjacent to the hilum or located in the periphery of



Case Illustration No 1 Patient J J

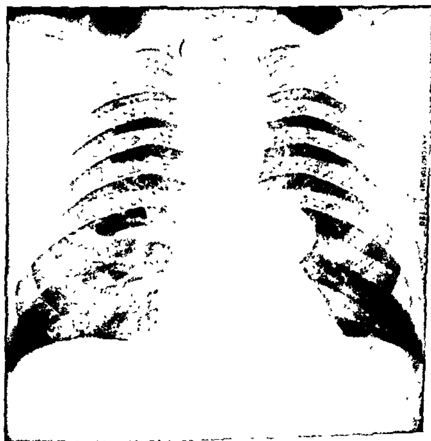
Fig 4B Roentgen examination, six years after resection, shows the right hemithorax filled by the remaining lobes There is no evidence of recurrence

the lung. The density may attain a fairly large size without losing its sharp definition. Not infrequently, there is present a second density due to atelectasis of the adjacent pulmonary parenchyma The majority of adenomas show some roentgen findings of significance. Tomographic studies are often very helpful in delineating the extent of the tumor mass.

CASE ILLUSTRATION No 2, PATIENT P. M. (Figs. 5A, 5B, 5C)

DIAGNOSIS Bronchial adenoma

SIGNIFICANT FEATURES History of recurrent hemoptyses of two years' duration, polypoid tumor visualized on bronchoscopy, left lower lobectomy, uneventful convalescence, full work tolerance five months post-operatively.



Case Illustration No 2 Patient P M.

FIG 5A There is a large homogeneous density extending from the left hilum The mesial portion of the density is obscured by the left border of the heart. The lung fields are negative.

SYNOPSIS Male, 45, hospitalized in January 1953 with history of sudden hemoptysis two years previously, episode of chills and fever six months later, and massive pulmonary hemorrhages two months before admission Physical examination disclosed an expiratory wheeze over the left lower lobe On roentgen examination, there was a sharply demarcated density in the left hilar region (A, B, C) Bronchoscopy showed a smooth polypoid mass occluding the left main bronchus, but biopsy was negative A presumptive diagnosis of adenoma was made and a thoracotomy was done on 12 January 1953 The left lower lobe and a portion of the medial wall of the left main bronchus were removed, completely excising the tumor Plastic closure of the bronchus preserved the left upper lobe

SURGICAL PATHOLOGY Gross examination of the specimen showed that the tumor was sharply circumscribed, grayish-white in color, and mottled with small



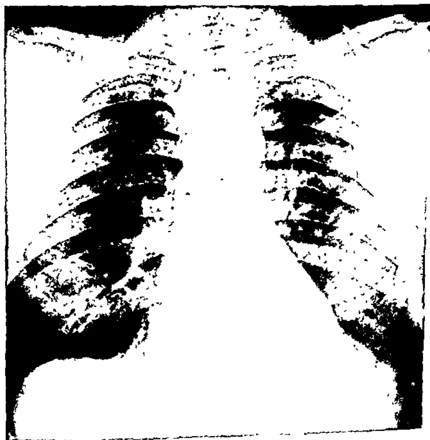
Case Illustration No 2 Patient P M

FIG 5B Tomogram, with section taken approximately 8 cm from the posterior chest wall, shows the density to be sharply circumscribed, ovoid in shape, and extending toward the midline

hemorrhages. The left lower lobe was partially compressed by the adenoma which was confined within its capsule. The bulk of the left lower lobe appeared normal On microscopic examination, the tumor was found to be composed of uniform-sized small cells arranged in a solid pattern.

DIAGNOSIS

The diagnosis of bronchial adenoma is established by the bronchoscopic examination Although a positive bronchoscopic biopsy is essential to confirm the diagnosis, visualization of the tumor usually reveals its distinguishing characteristics. The adenoma presents itself as a smooth rounded polypoid mass projecting into the lumen of a major bronchus. Depending on the degree of subepithelial vascularity, the color may vary from pink to



Case Illustration No 2 Patient P M

FIG 5C. X ray taken one year later *shows the left* upper lobe expanded and occupying the left hemi-thorax There is no evidence of tumor mass.

purple The tumor is often found completely occluding the bronchus of origin, and occasionally projects into the lumen of adjacent lobar bronchi Not infrequently only a small portion of the tumor is intrabronchial, and biopsy shows chronic inflammatory changes However, because of the hilar origin of most of the adenomas, the percentage of positive biopsies is high

The histogenesis of adenoma is responsible for the failure to obtain consistently biopsy specimens of diagnostic value The origin of the tumor from the sero-mucous glands below the surface epithelium results in an intact bronchial epithelium enveloping the growth, from which it is separated by an uninterrupted basement membrane and vascular connective tissue The biopsied fragment must, therefore, be obtained from tissue below the surface epithelium in order to contain elements of the tumor Other possible sources of error in interpretation are inflammatory metaplasia of the epithelium, and inflammatory and necrotic changes within portions of the tumor itself

Surgical Treatment

Resectional surgery is the principal mode of treatment of adenoma of the bronchus. Conservative limited resection of these tumors is based on

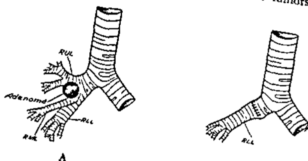


Fig 6

A Adenoma of right upper lobe bronchus, involving the anterolateral portion of the intermediate bronchus

B Tumor removed by right upper lobectomy, partial excision of the intermediate bronchus, and removal of the middle lobe Plastic closure of the bronchus preserved the entire right lower lobe

the fact that they are localized lesions, which may be potentially malignant, but which behave in a benign manner

The adenoma tends to remain confined within its capsule, even though it may achieve significant dimensions The line of surgical excision, therefore, may be quite close to the tumor Surgical therapy is not dependent upon the

histologic appearance, because all of the tumors are known to be *slow to* metastasize and slow to extend to adjacent structures. Endobronchial ade-

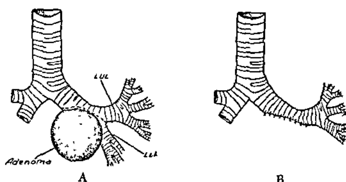


Fig 7

A Adenoma involving left main and lower lobe bronchi with proximal end about 3 cm. from the carina

B Tumor was removed by conservative excision and left lower lobectomy, which permitted plastic closure of the bronchus and preservation of the left upper lobe

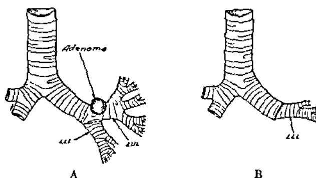


Fig. 8.

A Adenoma arising from anteromedial aspect of junction of left upper lobe and left main bronchus

B Tumor removed by lobectomy and segmental excision of the left main bronchus, end-to-end anastomosis preserved the left lower lobe.

noma frequently extends beyond the cartilages, with the major portion extrabronchial and projecting into the pulmonary parenchyma Its form may be compared to a dumbbell or, as is more often the case, an iceberg which has only a small fraction of its mass visible above the surface.

Each surgical approach should be taken with intent to resect the least amount of bronchus and lung tissue (Figs 6, 7, 8). All of the major vessels in the operative field should be dissected free so that they may be displaced, if necessary, to evaluate the local problem Temporary occlusion of the major vessels may be desirable to provide a clear field so that the confines of the tumor may be determined Resection is then started, excising only the necessary portion of the bronchus and lung Open airways may be controlled by tampons or the use of a Carlens tube The pre-operative and post-operative care is similar to that described in Chapter X Tracheotomy has proved of value in the protection of the end-to-end anastomosis of the trachea

Adenomas which have destroyed lung tissue by suppuration are treated by lobectomy, or pneumonectomy, as indicated Sleeve resection and end-to-end anastomosis is possible in the presence of a tumor of the main bronchus, and sacrifice of lung tissue may not be necessary Sleeve resection may also be accomplished with excision of a lobe or a segment Plastic closure of a bronchus after partial resection preserves considerable functioning tissue Tracheal adenomas may be excised by sleeve resection and end-to-end anastomosis after excision of up to five tracheal rings Partial resection of the tracheal wall has been successfully accomplished, utilizing plastics and stainless steel mesh for support

Endoscopic Treatment

The endoscopists were the pioneers in the diagnosis and treatment of this condition Because of the slow-growing nature of this tumor, many excellent results have been obtained by this mode of treatment It has become increasingly apparent, however, that the endoscopically treated tumors have tended to recur and have required repeated treatments In many instances the development of broncho-pulmonary suppuration distal to the tumor has required subsequent resection Despite the apparent simplicity of this form of therapy, there are definite hazards in the form of uncontrollable hemorrhage and fatal aspiration of large blood clots The endoscopic treatment of adenomas is adequate when the lesion is pedunculated and its base does not extend deep into the muscle coat or cartilages As the morbidity and mortality rates of resection have improved and plastic bronchial closure techniques have been perfected, endoscopic therapy has been reserved for selected cases.

Summary

The bronchial adenoma is a benign slow-growing tumor that tends to remain within the confines of its capsule Treatment is directed toward the excision of the tumor, removal of destroyed lung, and preservation of normal lung tissue In contrast to the surgical treatment of lung carcinoma, every effort is made to limit the extent of the resection Regardless of the

malignant potentialities of this tumor it behaves in a clinically benign fashion and this should be reflected in all surgical considerations The histological classification does not alter the *surgical philosophy of treatment*, which is based primarily on the extent of the tumor and amount of damage to the adjacent pulmonary parenchyma. Techniques of plastic bronchial closure have contributed much to the practical application of this attitude. Despite the time-consuming and meticulous technique required to accomplish limited resections it is a practicable procedure The operative mortality is negligible and recurrences are rare Secondary thoracoplasty is unnecessary and maximum lung function is preserved

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XII

Palliative Treatment

BERNARD ROSWIT, M D

The Need for Palliative Therapy

Limitations of Resectional Surgery The vast majority of patients with bronchogenic carcinoma, when first diagnosed, are already beyond hope for cure by surgical means The rapid increase in the incidence of lung cancer in recent years has not yielded a corresponding increase in the proportion of cases suitable for resectional surgery The contrast between the total number of lung cancer cases and the number suitable for resection is further emphasized by Smithers, who compared 13,000 deaths in England in 1951 with 250 pneumonectomies done that year This depressing picture is reflected in hospitals, in clinics, and in private practice throughout this country as well Recent advances in resectional thoracic surgery have been dramatic and gratifying indeed, but the over-all five-year survival rate is still less than 10 per cent

Limitations of Early Diagnosis During the past decade, the search for earlier cases of lung cancer has become more intensive, with vastly increased use of modern diagnostic techniques The results, thus far, have fallen far short of the expectation Despite the creation of many special diagnostic clinics, cancer education campaigns, and mass roentgen surveys, the yield of resectable cases is still depressingly low It is unrealistic to assume that their proportion will increase significantly in the near future The criteria for early clinical diagnosis held only a short time ago are now recognized to be actually pre-terminal manifestations Furthermore, most patients fail to seek medical advice until more than six months after the malignant lesion first announces its presence by obvious clinical symptoms Even then, suspicion may be lulled by the insidious character of this disease, masquerading as any one of a variety of benign disease entities

The present general interest in bronchial cancer has created a high index of radiographic suspicion regarding atypical pulmonary lesions and small

roentgen densities. In such instances, the Papanicolaou method of cytological diagnosis may be invaluable, but its application must be far more widely extended for more fruitful results Small lesions, however, even silent ones, are found to be associated with mediastinal involvement in about 25 per cent of cases Thus even the size of the lesion may bear no direct relation to resectability or survival.

Life History of the Disease As the inoperable malignant lesion pursues its course, there arises a symptom-complex that challenges the skill and resources of the family practitioner and specialist alike. The sequence and pattern of complaints is consistently and intimately related to the progressive life history of the malignant process—characterized by proliferation, endobronchial obstruction, pulmonary infection, local invasion, and finally, distant metastasis The untreated disease usually runs its course within less than two years from the date of diagnosis, ending with death from cachexia, metastases, hemorrhage, toxemia of infection, or cardio-respiratory failure

As the bronchial lesion proliferates, cough, dyspnea, wheezing, and hemoptysis present themselves as the earliest symptoms and become steadily worse When occlusion of a bronchus produces atelectasis and obstructive pneumonitis, the patient experiences fever, chills, malaise, anorexia, and weight loss Relief must be provided by re-establishment of adequate drainage through the bronchial lumen, as well as by control of pulmonary infection Rapidly growing peripheral tumors arising from the smaller bronchial channels are prone to central necrosis and abscess formation Dysphagia not infrequently results from pressure of the primary tumor or metastatic lymph nodes upon the esophageal lumen Intractable pain and disability arise from invasion of the thoracic cage, spinal column, or bones of the extremities Extension to the pleura is nearly always accompanied by massive pleural effusion, demanding repeated thoracentesis or more effective means of control.

The superior vena cava compression syndrome, which occurs in about 15 per cent of the cases, requires prompt relief from intractable cough, dyspnea, orthopnea, vertigo, and grotesque swelling of the head and neck Unless this complication is effectively controlled death will follow quickly. Patients who experience encroachment of the cervico-brachial nerve plexus and the thoracic cage by superior sulcus tumors are often in desperate need of relief from relentless pain When the liver is finally invaded, the slender period of survival is further burdened with suffering from abdominal pain and distention, prostration, and toxemia.

Treatment Policy

General Considerations Prompt symptomatic relief is the principal aim of all palliative therapy Successful palliative measures should afford a relatively long interval of comfort in proportion to a short period of terminal

illness even though the over-all survival period may not be significantly improved (Tod) This is accomplished most effectively in the majority of cases by means of *palliative* roentgen therapy—with chemotherapy, palliative surgery, and radio-isotopes as helpful adjuncts Relief of distress and disability is often accompanied by objective evidence of temporary improvement.

Prolongation of survival time in the inoperable case, with restoration of the individual to family, social, or economic usefulness, is a far more elusive goal. At present, the only hope for achieving this aim lies in applying *radical* roentgen therapy to a selected group of inoperable patients, as early as possible in the course of the disease

Improvement of survival time has been reported from several radiation clinics, both here and abroad (Brooks, Davidson, Thomas, Robson and Smithers, Hare and Trump, Craver, Haas, Harvey, and Langer, Widman, Leddy, Dobbie, Taylor, and Felton) Reports of five-year survivals in histologically proven cases have been documented Borne reported four patients with epidermoid cancer surviving five years after radiotherapy, two of which had lymph node invasion at operation Leddy at the Mayo Clinic reported the survival of 25 of 125 treated patients, all histologically confirmed, for periods from two to twelve years

Brooks and his colleagues, in evaluating the results of a five-year study of 502 patients with bronchial cancer, came to the conclusion that the palliative value of X-ray therapy was most marked It held out the only regular means of symptomatic relief in the majority of patients who came to the hospital Smithers, recently reviewing his experience with 192 irradiated patients, concluded that too many general practitioners, remembering the time when irradiation sickness was commonplace and local reactions were severe, seem to be far too ready to deny their less debilitated patients the benefits of radiation treatment Radiotherapy is shouldering the burden of treatment to an increasing degree, but is still not sufficiently available to all who need it Sufficient experience has accumulated in recent years to support the presentation of a positive treatment program While universal agreement on the details of such a program will probably never be attained, there is at least provided a broad and reasonable basis for clinical application

OUTLINE OF TREATMENT POLICY

1 *Surgical Resection* For all operable cases, whenever feasible.

   a The operable patient should not be offered a choice between radical surgery and radical radiation therapy Once the diagnosis is firmly established the best chance for cure in operable cases lies in surgical resection In cases of doubtful diagnosis early exploratory thoracotomy should be promptly undertaken

b When nonresectable mediastinal invasion is encountered at operation, the tumor-bearing lobe or lung may be resected if possible, to be followed promptly by post-operative roentgen therapy.

2 *Palliative Roentgen Therapy* For inoperable cases when—

a Patients are unsuitable for radical roentgen treatment because of extensive intrathoracic lesions, distant metastatic foci, or unsatisfactory general condition

b Patients require prompt relief from symptomatology arising from endobronchial obstruction, esophageal compression, the superior vena cava compression syndrome, skeletal invasion, cerebro-spinal metastases, or other manifestations of rapidly advancing malignant disease

3. *Radical Roentgen Therapy:*

a. For *operable* cases when—

(1) Surgery is adamantly refused by the patient.

(2) Operation is unfeasible for medical reasons, such as cardiac disease or other complications

(3) The primary lesion is not resectable.

(4) The primary lesion has been incompletely removed.

(5) The primary lesion has been completely removed but nonresectable regional lymph nodes remain.

b For *inoperable* cases when—

(1) The lesion is intrathoracic, unilateral, and not extensive, in patients whose general condition is fair.

(2) The tumor is of borderline operability and may become operable after roentgen therapy.

(3) There is local recurrence after surgical resection

4. *Nitrogen Mustard Therapy* For *inoperable* cases when—

a Roentgen therapy becomes no longer feasible or effective because of widely generalized disease, radio-resistant tumor, or untoward reactions to radiation

b Control of severe constitutional symptoms will make the patient acceptable for more effective therapy with radiation

c Superior vena cava compression syndrome or cerebro-spinal complication demands immediate relief. In such cases, nitrogen mustard should be quickly followed by more definitive treatment with roentgen radiation.

5. *Radio-isotope Therapy*

a. For *inoperable* cases when—

(1) Recurrent pleural effusion becomes a pressing problem.

(2) Accessible metastatic lesions no longer respond to roentgen therapy or nitrogen mustard.

b For operable cases when—
(1) Malignant tissue contaminates the pleural space.
(2) Hilar or mediastinal lymph nodes prove to be nonresectable
6 *Other Medical and Surgical Palliative Measures* For patients with intractable pain, infection, toxemia, or neuro-psychiatric complications

Palliative Radiation Therapy

All patients with nonresectable lesions must sooner or later require relief from intractable symptomatology Roentgen therapy is the most valuable means for providing such relief. Experience indicates that when an effective palliative tumor dose is administered (approximately 3,000r in 3 weeks) the majority of patients experience relief from cough, chest pain, expectoration, hemoptysis, dyspnea, orthopnea, bone pain, or dysphagia There may be objective evidence of temporary improvement, characterized by relief of bronchial obstruction, clearing of obstructive pneumonitis, regression of parenchymal lesions, shrinkage of metastatic lymph nodes, and regression of the superior vena cava compression syndrome A satisfactory response to therapy may first be noted in from two to three weeks after treatment has been instituted In highly anaplastic lesions, the response may be more prompt and striking This is often followed by gain in weight and strength The improvement may last from several weeks to several months and, occasionally, for even longer periods (Fig 1A–D, Fig 2A–D) The treatment course may be repeated once in the same area, if necessary

Untoward local reactions in the palliative dose range are usually minimal and easily controlled They rarely constitute an obstacle to completion of a well-planned and well-executed course of treatment Patients in a severely cachectic and pre-terminal state, however, respond poorly and are unsuitable for roentgen therapy Necrotizing lesions and those severely infected, with abscess formation, respond poorly and should not be irradiated

It is not always possible to provide a strict distinction between palliative and radical radiation therapy Sound clinical judgment and experience must govern the selection of patients, the choice of objectives, and radiological management By the time many patients are referred for treatment only palliative tumor doses (3,000r in 3 weeks) are advisable or even feasible The status of these individuals usually precludes serious consideration for more radical treatment involving a tumor dose level of approximately 5,000r to 6,000r in 5 to 6 weeks Palliative roentgen therapy must nonetheless be well planned and administered with precision and well-defined objectives Too often, the radiologist is asked to give 'just a few treatments'—resulting, almost invariably in failure

When atelectasis and obstructive pneumonitis follow closure of the airway, relief can be provided by means of a treatment portal carefully directed



FIG 1 *Radiological and Clinical Results of Radical Roentgen Therapy.*

Case 1

A Note massive primary lesion with involved hilar and mediastinal nodes 68-year-old male veteran with epidermoid carcinoma, right upper lobe bronchus, associated with hemoptysis, cough, and atelectasis.

B. Same patient, after 6,048r tumor dose in 55 days, cross-fire technique, conventional machine Note complete disappearance of atelectasis, primary lesion, and metastatic lymph nodes. Symptomatic relief lasting nearly a year.

Case 2.

C Note complete opacification of the left hemi-thorax, indicating massive atelectasis left lung 63-year-old painter, with epidermoid carcinoma, Grade 3, in-

Continued on next page

to the site of endobronchial obstruction As soon as the integrity of the bronchial lumen is re-established, prompt postural drainage and the use of antibiotics can be very helpful Intracranial lesions are observed in about 10 per cent of the cases Although these cases respond for only limited periods, the restoration of neurological competency is no small achievement Treatment must be instituted promptly after recognition of this complication. Small initial tumor doses (75r to 100r) are indicated for the first several days to avoid inducing edema and further complicating the problem In very rapidly progressing lesions, surgical decompression is imperative prior to the initiation of roentgen therapy

Relief from the superior vena cava compression syndrome is one of the most gratifying and dramatic results provided by palliative roentgen therapy (Fig 2c and D) The onset of this complication is an ominous event and occurred in 15 per cent of our cases Unless decompression by roentgen therapy is promptly and effectively instituted, the patient's course is rapidly progressive, ending in cerebral anemia, anoxemia, failure of the respiratory center, and strangulation edema of the glottis and respiratory passages Relief can be promptly provided in three out of four cases with an average remission of 14 weeks after a single course of therapy (Roswit, Kaplan, and Jacobson). In a few instances, the remission may last from six months to a year. These results may be a reflection of the fact that 90 per cent of the lesions giving rise to this complication were of a highly undifferentiated histological type Nitrogen mustard is a valuable adjunct and can be used to advantage before radiation treatment Improvement with nitrogen mustard is often more prompt than with X-ray therapy, but is not as lasting The average remission from the drug was three and a half weeks, compared to three and a half months for X-ray therapy (Roswit, Kaplan, and Jacobson) Wood also noted that, of 20 patients with superior mediastinal obstruction, there was complete disappearance of the signs in 12 and diminution in 4 others after radiotherapy

Patients presenting the Pancoast syndrome, with invasion of the cervicobrachial plexus and the thoracic cage, generally respond poorly to roentgen therapy, but deserve a trial of radiation because of their extreme distress Haas, Harvey, and Langer have recently reported several such patients who responded unusually well to betatron X-ray therapy, with complete disappearance of invasive tumor and restoration of useful activity

In situations allowing the use of no more than a single large portal, lead-rubber grid technique or supervoltage therapy (1–2 Mev radiation) is distinctly helpful in avoiding untoward skin reactions The skin dose through

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volving the left main bronchus, associated with cough, hemoptysis, dyspnea, chills, and fever

D Same patient after 5,800r in 38 days Note complete clearing and aeration of left lung field Disappearance of all complaints now lasting three months



FIG 2 *The Superior Vena Cava Compression Syndrome—Clinical and Radiological Results of Therapy*

A Infra-red photograph of elaborate superficial venous collaterals in a patient with superior vena cava obstruction at a point *above* the entry of the vena azygos.

B Angiocardiogram revealing opacification of right sub-clavian and internal jugular vein, joining the right innominate vein, but the superior vena cava is blocked Note the striking degree of superficial collateral circulation via intercostals en route to azygos vein and right auricle.

Case 3.
C Note massive primary lesion and metastatic lymph nodes 57-year-old coal miner with brief history (one month) of dyspnea, orthopnea, swelling of head and neck, and extensive superficial collateral vessels on the trunk Anaplastic epidermoid carcinoma, right upper lobe bronchus.

Continued on next page

the small grid openings should be limited to a maximum level of 15,000 roentgens.

RADICAL ROENTGEN THERAPY

Bronchogenic carcinoma is a radio-responsive neoplasm similar to those encountered in the cervix, bladder, oral cavity, tonsil, larynx, and pharynx. In recent years, it has become feasible to deliver an aggressive dose of radiation to this deep-seated lesion and its regional nodes with minimal trauma to the skin, and without severe systemic symptoms, but the tissue tolerance of the normal lung remains a critical limiting factor. Nevertheless, one may enhance the inoperable patient's chance for prolongation of comfortable life through radical roentgen therapy in selected cases.

This observation has been well documented in many radiation clinics. For example, Smithers reports that of 192 inoperable patients who received radical therapy, 12.4 per cent survived from two to seven years after treatment. One patient was still alive after seven years. Brooks and his colleagues report that of 126 inoperable cases radically treated 18.4 per cent survived from two to five years. Untreated patients seldom survive more than two years after the diagnosis is established. There is sometimes evidence at necropsy of complete eradication of the intrathoracic lesion after intensive radiotherapy (Churchill, Brooks *et al*, Fried, and others).

Within the past five years, the striking technical advances in radical chest surgery have been paralleled by the development of radiological techniques for delivering intensive radiation to deep-seated chest tumors with ease and precision. Supportive chemotherapy and antibiotics have contributed in no small measure to our ability to provide a more aggressive attack upon the malignant growth. While the individual appears quite able to sustain such intensive local radiation, the tolerance of the lung itself imposes a limitation upon doses at cancerocidal levels. In this dose range, radiation pneumonitis may be encountered. Skillful treatment planning, steroid therapy, and broad-spectrum antibiotics give promise of effectively ameliorating the ill effects of this complication (Cosgriff and Kligerman, Friedenberg and Rubenfeld, Whitfield, Bond, and Arnott).

Since the progressive annual increase in new cases is great and the proportion of surgically resectable cases remains low, roentgen therapy should be provided with every opportunity to prove whether or not it can provide longer life in a greater percentage of the nonresectable cases. This can be

D. Same patient after 3,500r to the tumor in 51 days. Note almost complete disappearance of the massive primary lesion as well as metastatic hilar and mediastinal nodes. A remission of one year followed this single course of roentgen therapy.

(Courtesy *Radiology*, November 1953, 61, 722, Roswit, B., Kaplan, G., Jacobson, H. G.)



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accomplished only if a substantial number of such patients are promptly referred when still in good general condition, with minimal symptomatology, relatively limited intrathoracic disease, and no clinical or radiographic suspicion of distant metastases. In recent years we have employed radical roentgen therapy in other malignant lesions of borderline inoperability, with the expectation that some of these might become operable. This program has met with gratifying results in neoplasms of the head and neck. Of unusual interest is the report of Wood, that of eleven patients with bronchial cancer appraised as inoperable before treatment, five became operable after radiation therapy and had pneumonectomies performed

Within certain limits, higher doses produce more effective clinical results (Fig 2A–D). Although an optimal tumor dose and treatment time in radical therapy has not been established, a level of 5,000 to 6,000 roentgens in 5 to 6 weeks appears satisfactory. To deliver this tumor dose with conventional apparatus, it becomes necessary to utilize to the best advantage multiple portal cross fire techniques, grid therapy, or rotation methods in order to avoid intolerable reactions Supervoltage radiation (1 MEV, 2 MEV, 22 MEV) and telecurietherapy (Cobalt 60), when available, offer considerable physical and clinical advantages. A more homogeneous tumor dose may be there attained with relative ease, as well as a marked reduction in local and systemic reactions.

Treatment Planning As in radical cancer surgery, there can be no excuse for a quality of radical radiation therapy which falls in any way short of the highest achievement possible Substantial advances have been made in *recent years in tumor localization, understanding of tissue tolerance, the* physics of treatment planning, X-ray engineering, precisional beam orientation, rotational techniques, and mould technology. A well-planned program *for radiation treatment of deep-seated cancer* utilizes these advances to maximum advantage. The important elements in such a program may be briefly outlined as follows.

1. *Consultation*· The objectives of treatment (radical or *palliative*) are determined only after a critical appraisal of the patient's general condition, extent of his disease, and histology of the lesion. For example, a cachectic patient *with an extensive lesion, particularly if it* is necrotizing, is a poor subject for aggressive treatment An intensive therapy schedule is hardly indicated for the individual with an oat-cell tumor, *because of its striking* radiosensitivity and its propensity for rapid distant metastases No radical therapy should be planned without unequivocal histological or cytological evidence of bronchogenic carcinoma Since one cannot predict with certainty the radiologic response in a particular histological type, a test of radiosensitivity should always be undertaken when an ul situation exists.
2. *Tumor locali-* n of the location of the bronchial tumo *by bronchoscopic and*

radiographic methods, utilizing lipiodal, implanted radon seeds (inactive), metal clips, fluoroscopy, localizing tapes and grids, and horizontal and vertical body-section roentgenography External landmarks are recorded on the skin. An impression is made of the external body contour through the principal plane of the tumor, and other planes when indicated, employing plaster bandage impregnated with a fast-setting plastic compound (Fig. 3A, B) The contour is then transcribed onto a planning sheet (Fig 3C) The site of the tumor and critical anatomical structures such as lung, spinal cord, and esophagus are drawn on this life-size cross-section drawing of the patient (Fig 3C).

3 *Prescription-biological* The tumor dose (maximum, minimum, and average) is prescribed, as well as the treatment time (in over-all days) The maximum permissible dose is prescribed for skin, normal lung, spinal cord, esophagus, and other important normal tissues in the path of the beam The radical tumor dose may be approximately 5,000r to 6,000r in 5 to 6 weeks

4 *Prescription-physical* Isodose charts of the appropriate field size are applied to the cross-section diagram of the patient (Fig 3D), and the optimum treatment technique for the particular patient is thus evolved (Fig 4A, D) On the basis of the patient's requirements and the technical facilities available, one may select a multiple portal cross fire method (Fig 4A), grid method with paired-opposing portals (Fig 4B), rotational or scanning technique (Fig 4C), or supervoltage X rays (Fig 4D)

5 *Fabrication* A treatment shell of plaster bandage is rapidly fabricated (Fig 5D), reproducing accurately the prescribed treatment plan This shell provides three-dimensional treatment planning, immobilization of the patient, accurately defined and fixed treatment portals, daily reproducible beam-alignment, and application of bolus when required In supervoltage therapy, however, the interposition of any material on the skin surface in the portal area cancels out the skin-sparing effects of high voltage radiation

6 *Application* In delivering the treatment, strict attention is given to precisional beam orientation, utilizing beam directors, back-pointers, light localizers, pin-and-arc units, and similar devices when indicated (Fig 5A–D) Radiographic confirmation of the accuracy of the beam alignment is regularly secured

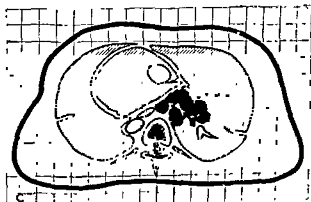
7. *Observation* During the course of therapy, the effects of radiation upon the tumor, the normal tissues, and the patient as a whole are daily observed and charted Complications are thus promptly recognized and ameliorated The prescribed treatment plan may be promptly modified when indicated Serial histological and cytological material (Papanicolaou method) may be secured at regular weekly intervals to assist in evaluation of the immediate radiological response. The clinical



FIG 3 *Planning System for Radical Roentgen Therapy*

A. Localization film showing principal plane through tumor site. Precise definition of tumor is best accomplished by bronchoscopy, fluoroscopy, body-section radiography (vertical and horizontal), and contrast radiography (with lipiodol, inactive radon seeds, and metallic clips).

B Recording of body contour through principal plane of tumor by means of fast-drying plaster bandage dipped in plastic composition, and molded to patient's body Plaster body shells are prepared in similar manner for three-dimensional treatment planning, immobilization of the patient, and precise daily beam-orientation.



C Planning Sheet illustrating patient's cross-section, tumor site, and critical anatomical structures, ready for the prescription of dose, time, portals, and other technical factors.

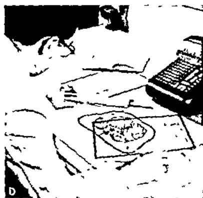


Fig 3 *Continued*

D. Translucent isodose patterns are applied to determine the optimum physical treatment plan for this particular patient The objective is to deliver a homogeneous cancerocidal dose to tumor with minimal radiation damage to critical normal tissues

management of the patient during his radiation course is best accomplished by close collaboration between the therapeutic radiologist and the referring physician

Rotational Therapy Rotational therapy apparatus (horizontal and vertical) may be utilized with standard 180 to 260 kv equipment for radical treatment of deep-seated cancer, including bronchogenic neoplasms (Figs 4c, 5c (Nielson; Kligerman, Rosen, Quimby, and others) In this manner aggressive tumor therapy can be delivered with less damage to the skin and other normal tissues in the path of the beam Such equipment has been in operation in our clinic for the past two years and has proved to be a valuable therapeutic adjunct (Fig 5c) Within the past year apparatus has become available providing standard X-ray tubes rotating about a central axis with the patient in the horizontal position Rotation therapy may be regarded as the maximum utilization of the multiple beam cross fire technique, providing an infinite number of entry portals In addition to complete rotation, scanning has also been used advantageously in some cases, in combination with fixed fields Critical tissues, such as the spinal cord, may be well protected by the use of lead strips, just as in stationary fields The possible arrangements and combinations in treatment planning become practically infinite in variety Experience leads us to believe that rotation therapy actually offers greater relative advantages in combination with conventional therapy apparatus, than with very high energy equipment or telecurietherapy units.

Grid Technique A lead-rubber grid makes it possible to deliver radical dosage to deep-seated lung cancer with greater facility, using standard X-ray apparatus (Figs 4B and 5B) This technique has been referred to as 'the poor man's supervoltage equipment' The hazard to the skin is reduced by limiting the skin damage to small, circular, open areas in the lead-rubber shield. The recent reports of Harris, Marks, Loevinger, Jacobson, Sopp and

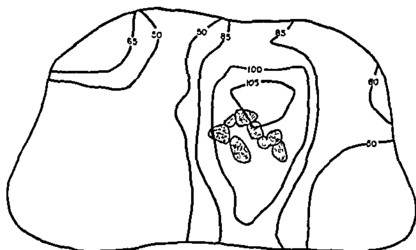
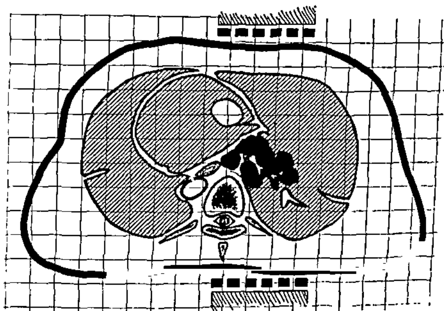
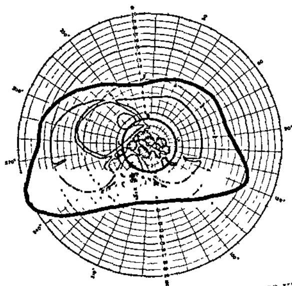


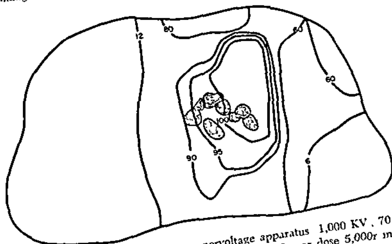
Fig 4 *Typical Treatment Plans for Radical Roentgen Therapy.*
A. Multiple portal cross-fire plan for conventional apparatus. 260 KV, 70 cm tsd, 2 5 mm. Cu HVL, Thoraeus filter, 4 portals—8 × 12 cm. each Tumor dose, 5,000r in five weeks, skin dose. 4,200r Radiation to normal tissues within tolerance limits Skin reaction moderate and tolerable Homogeneity of radiation to tumor Compare with Fig 2D



B. Grid plan for conventional apparatus 260 KV, 1.5 mm. Cu HVL 50 cm tsd, 8 × 12 cm paired opposing portals Tumor dose 5,000r in 5 weeks, employing an air dose of 13,550r Although the skin under each opening receives 15,000r, the skin covered by the lead-rubber is well protected, receiving only 2,400r. Thus it becomes feasible to deliver a lethal tumor dose with conventional apparatus, without intolerable damage to the skin.



C Rotational treatment plan for conventional apparatus 260 KV, 85 cm target-axis distance, 1 5 mm Cu HVL, 8 × 12 cm portal Objective is to deliver a tumor dose of 5,000r in five weeks with minimal damage to skin (3,375r), spinal cord, and intervening lung tissue Only moderate skin erythema noted Note special planning sheet of polar coordinate paper



D Multiple portal cross-fire plan for supervoltage apparatus 1,000 KV, 70 cm tsd, 3 9 mm Pb HVL, 3 portals—8 × 12 cm each Tumor dose 5,000r in five weeks with 4,100r on the skin Smaller volume dose for same tumor dose results in fewer local and systemic reactions Only slight skin erythema with bronzing Greatest homogeneity of radiation through tumor area

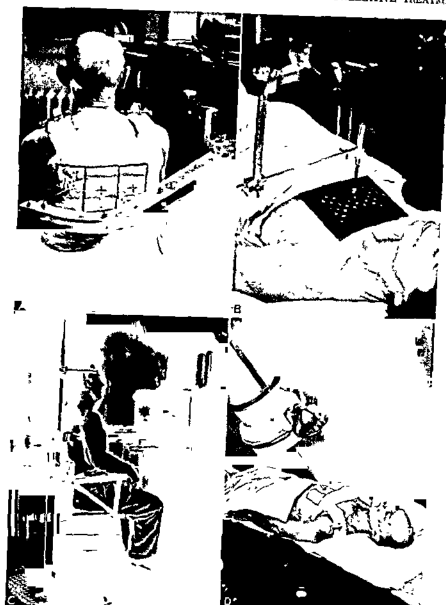


FIG. 5 *Treatment Techniques for Radical Roentgen Therapy.*

A Precisional cross-fire technique with conventional apparatus utilizing 'back-pointer' to assure daily reduplication of accurate beam-orientation

B Grid technique, utilizing Marks lead-rubber grid, for use with conventional apparatus (200–260 KV), generally referred to as 'the poor man's supervoltage apparatus'

Continued on next page.

Stanton, and others, have added greatly to our understanding of this useful technique and its clinical applications Our own experience with this method in 50 patients suggests that it deserves to become firmly established as a useful adjunct in the treatment of inoperable lung cancer, when standard X-ray equipment is on hand Skin dose levels should not exceed 15,000 roentgens

Supervoltage X rays and Telecurietherapy (Cobalt 60) Within the past few years, there have been unusual advances in the development of super-voltage X-ray apparatus (1 MV, 2 MV, 22 MV), as well as telecurietherapy equipment utilizing high intensity sources of Cobalt 60 This radio-isotope emits a gamma ray beam equivalent to that produced by a two-million-volt X-ray generator—with most of its physical and clinical advantages and few of its disadvantages High energy X-ray machines and kilocurie nuclear sources provide an increase in the quality or hardness of radiation, with greater 'reaching power' for deep-seated tumors, minimal skin reactions, relatively less bone damage, and remarkably little radiation sickness Patients may be treated with greater speed and facility

Fried and Tenzel have treated more than 75 inoperable lung cancer cases using a Cobalt 60 unit Their patients tolerated the treatment well and delivery of the radical tumor dose posed no serious problems Their clinical results were definitely improved, when compared with those achieved with conventional apparatus Hare treated 43 cases with two-million-volt X rays, directing therapy to include the mediastinum, the pulmonary lesion, and the supraclavicular areas Doses up to 6,000r were delivered in 35 treatments Favorable results were obtained in about 50 per cent of the total group Watson and Burkill, Harvey and Haas have reported marked subjective improvement and prolongation of useful life in advanced cases using the 22 million volt betatron One of the cases treated by Harvey, suffering from the Pancoast type of tumor, is living and well thirty-four months after irradiation Intractable pain gradually disappeared during the course of treatment and rib destruction spontaneously recalcified

High energy radiation is indeed preferable, when available, but worthwhile benefits will continue to be achieved with standard X-ray therapy (180 to 260 kv), by careful selection of patients, well planned treatment, precisional delivery of effective dosage, and control of complications

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C. Rotation therapy technique for use with conventional 200–260 KV machine Optimum technique for certain deep-seated bronchogenic cancers

D. Precisional cross-fire supervoltage technique, utilizing Roswit Beam Director on machine-head and Demy Localizer over patient's chest In practice, no plaster material is interposed in the path of the beam in the actual portal area

(Illustrations C and D reprinted from N Y S J Med, July 1953, 53, 1647, 'Palliative treatment of non-resectable pulmonary neoplasms—primary and metastatic,' Mayer, E, Roswit, B)

RADIATION REACTIONS

The impact of ionizing radiation on living tissue is entirely destructive in nature. Its effectiveness in cancer therapy is wholly dependent upon the *differential between the radiosensitivity of the tumor and the limits of* tolerance of the normal structures, including the host. Although bronchogenic carcinoma is a radio-responsive neoplasm, clinically effective doses cannot be delivered without some degree of reaction in the skin, lung, other intervening tissues, and in the individual as a whole. It is therefore un-*reasonable for the referring physician to expect every patient who receives* palliative radiation therapy to be spared its transient and minimal discomforts Not infrequently, patients are *peremptorily withdrawn from the treat-*ment schedule by the referring physician because of undue alarm and apprehension over a brisk erythema of the skin or a moderate degree of radiation sickness, each reversible and easily managed with appropriate medical care In radical roentgen therapy, however, moderate to severe reactions, *both local and systemic, may attend the administration of higher tumor dose* levels. They may appear quite strange and alarming to the already apprehensive cancer patient, unless he has been adequately informed and reassured prior to initiation of treatment

With 200 to 260 KEV radical radiation, the primary erythema gives way to a moist desquamation or secondary erythema This should never be referred to as a 'burn,' bearing the implication of an unfortunate and prevent-*able accident. This radiation reaction, too, will heal, requiring only* the simplest of hygiene during the acute phase. The late changes, including scarring, atrophy, and telangiectasis, are rarely a source of discomfort A valuable clinical guide to skin tolerance, in relation to dose, time, and portal size, has been provided by Paterson When supervoltage radiation is employed, only a moderate primary erythema and bronzing are observed, even when skin doses approaching 7,000 roentgens have been delivered

Radiation sickness, when it occurs in radiotherapy of intrathoracic lesions, is characterized by loss of appetite, nausea, vomiting, and weakness With 200 to 260 KEV radical radiation, about 70 per cent of the patients may be expected to experience one or more of these symptoms to a greater or lesser degree A clinical guide to the factors which influence the incidence and *severity of the syndrome has been provided (Ellinger, Boswit, and Sor-rentino).*

The systemic syndrome can be promptly and effectively controlled in [illegible] experience, has rarely constituted an obstacle to [illegible] therapy, nor has it often required serious modification of the planned course of treatment Within twenty-four to thirty-six hours after completion of the

radiation schedule, there are no residual symptoms. With supervoltage therapy, patients complain only infrequently of radiation sickness

Acute and chronic reactions in normal intervening lung tissue may be expected in radical dose therapy of intrathoracic neoplasms Although there are striking individual variations in pulmonary tissue tolerance, the incidence and severity of such reactions is augmented with increase in the total dosage, the daily radiation intensity, and the volume of the irradiated tissue There is yet no reliable guide to the tissue tolerance of the normal lung, although it is suspected that it parallels that of the skin Excellent reviews of radiation reactions in the lung have been published by Warren and Spencer, Warren and Gates, Fried and Goldberg, Engelstad, Bergman and Graham, Spitz, and others

The onset of the acute or 'wet' reaction may occur at the height of the skin erythema, or shortly after completion of a course of radiation It is characterized by a diffuse pneumonitis of non-specific nature, sharply limited to the irradiated area The patient may experience a dry cough, chest pain, low grade fever, dyspnea, and malaise In most instances, however, there may be little in the way of symptoms and the reaction may be entirely overlooked A radiograph at this time will reveal a hazy or streaky infiltration often fanning out from the hilum, accurately defining the treatment portal These roentgen findings may be misinterpreted as tumor extension, and radiation therapy is intensified

In most cases, the pneumonitis will subside, leaving little or no fibrosis or functional impairment When the reaction is severe and covers a wide area, f[illegible]me more pronounced and functional impairment [illegible]therapy Extensive fibrosis, pleural adhesions, and cont[illegible]ay be late residuals of the severe reaction, and will be seen betw[illegible] 24 months after completion of treatment Pneumonectomy for late pulmonary fibrosis has been successfully performed in patients whose tumors were eradicated by radical treatment (Burnett, Dotter and Steinberg, Bergman and Graham)

If radical radiation is to make a real contribution to the treatment of cancer of the lung, every consideration must be given to measures for avoiding or minimizing severe pulmonary reaction, acute or chronic Within our present knowledge, the most important of these measures include avoidance of hyperintensive total tumor dose, hyperintensive daily tumor dose, massive treatment portals well beyond the tumor site (precise tumor localization must therefore be pursued with every available means), radiation 'hot-spots' where X-ray beams intersect (treatment plans, utilizing isodose patterns should be carefully reviewed to reduce the number of such hazardous areas), irradiation of severely infected lung tissue (intensive treatment with broad-spectrum antibiotics is indicated prior to and during radiation therapy in such cases) and treatment of patients with an already badly compromised pulmonary reserve

The possibility of preventing or ameliorating pulmonary reactions through steroid therapy has recently engaged the attention of several investigators (Cosgriff and Kligerman, Friedenberg and Rubenfeld; Whitfield *et al*) These clinical investigations were based on reports describing the ability of cortisone and ACTH to inhibit fibroblastic proliferation which occurs following trauma to tissues in experimental animals (Ragan *et al.*, Spain, Molomut and Haber, Shapiro, Taylor and Taubenhaus; Scheinberg and Saltzstein) Animals subjected to severe trauma show a striking depression in new growth of all elements of connective tissue and decrease of granulation tissue. Furthermore, a variety of chronic pulmonary diseases in humans has been favorably influenced by cortisone, with resolution of the pathologic process and increase in the oxygen diffusing capacity of the lung

Cosgriff and Kligerman reported the first favorable clinical response to ACTH and cortisone in a patient who developed acute radiation reaction of the lung. Marked subjective and objective improvements were described, with reversal of the acute pneumonitis. Freidenberg and Rubenfeld recently reported a trial of cortisone in prophylactic therapy. Nine patients receiving intensive radiation (up to 8,000r tumor dose) were given cortisone (100 mgm daily) throughout the period of therapy and for two weeks thereafter These patients have now been followed up to fifteen months after treatment, and in not a single instance was a pulmonary reaction noted Rubenfeld has been administering cortisone (100 mgm. daily) during and long after radiotherapy to more than 50 patients receiving radical treatment for bronchogenic carcinoma These individuals have been followed for periods up to eighteen months, and there has yet been no instance of severe radiation pneumonitis or fibrosis It is of further interest that cortisone, during the rigorous regime of therapy, appeared to improve the patient's general well-being, appetite, and morale, and controlled the symptoms of radiation sickness.

Nahon has recently emphasized the need for reorientation of our present method of dosage determination, with particular reference to radiation of intrathoracic lesions Measuring the exit dose in a large number of patients, he found a wide variation in exit dose levels for the same thickness of similar body regions in different individuals Differences of the order of 250 per cent were found in the thorax. Each patient therefore represents a separate radiotherapeutic problem. Clinical evaluation of the probable tissue capacity for transmission of X rays, together with the radiotherapist's experience, should serve as a guide in modifying calculations based on standard tables

One must consider the reactions of other tissues in the thorax, such as bones, myocardium, blood vessels, spinal cord, although serious complications in these sites have been rarely encountered With hyperintensive and oft-repeated irradiation, the bones of the thoracic cage may undergo rarefying osteitis, characterized by circular areas of absorption and fractures with non-union These may be misinterpreted as bony metastases and receive

further irradiation The myocardium is relatively radio-resistant to radiation, and untoward reactions in the heart and great blood vessels have not been reported However, smaller blood vessels may occasionally be heavily damaged, with subsequent hemorrhage In most cases intensive therapy to the thorax is sustained without any impairment of hematopoietic function Occasionally, a transient leukopenia may develop in the third to fourth week of therapy, returning to normal levels without interruption of the treatment schedule On rare occasions, patients may be observed with an unusually sensitive bone-marrow, and supportive measures must be instituted or treatment actually abandoned

Radiation damage to the spinal cord has been rarely reported, and for this reason, the impression has been gained that this tissue is relatively radio-resistant Boden has directed attention to the fact that post-radiation myelitis may develop when long sections of the cord are subjected to dose levels greater than 3,500 roentgens in seventeen days Treatment plans must therefore be so conceived as to spare the spinal cord as far as possible, with careful and routine estimates of the dose to this critical tissue Symptoms may arise approximately twelve months after treatment, with a range from one to fifteen months. They consist of numbness and paraesthesias of the extremities, which may be transient in nature and of relatively little importance in relation to the malignant lesion being treated However, there is danger in the possibility that these symptoms may be ascribed to metastasis and additional radiotherapy administered When a hyperintensive dose has been delivered, premonitory symptoms will be followed by weakness and paralysis of the extremities, and bowel and bladder dysfunction The true nature of this complication should be suspected if the motor and sensory signs and symptoms are referable to a segment of the cord included in the treatment portals

Nitrogen Mustard Therapy

Indications Nitrogen mustard is a useful systemic adjunct to roentgen therapy in the management of inoperable bronchogenic carcinoma, but it should never be employed as a substitute for X-ray therapy It is particularly helpful when radiation is no longer feasible or effective, because of far advanced and widely generalized disease, severe constitutional symptoms, radio-resistant cancer, or fulminating superior vena cava compression syndrome HN_2 (methyl-bis beta chloroethyl amine hydrochloride) has been widely used in this country and abroad (Gilman, Goodman, Jacobson, Karnofsky, Roswit, Kaplan, and others) It is a powerful systemic toxin with a special selectivity for actively proliferating tissues The physiological action is remarkably rapid, the lungs receiving the full impact of the agent after intravenous injection The minimal histological changes observed in the tumor resemble those seen after small doses of ionizing radiation

Clinical Results Experience with forty patients in whom roentgen therapy was no longer feasible or effective has shown that thirty of these individuals enjoyed respites from discomfort averaging one month, and in a few instances up to five months, after a single course of HN_2. Repeated courses—at one-month intervals—became less and less effective in relieving cough,

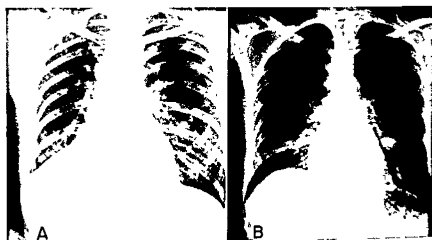


FIG 6 *Nitrogen Mustard Therapy—Clinical and Radiological Results*

A. Note atelectasis right lower lobe, metastatic deposits in both lung fields, and enlarged mediastinal nodes Carcinoma of right lower lobe bronchus in male veteran, age 40 Patient had intractable dyspnea, pain, fever, chills, and anorexia Too ill for transportation to Radiotherapy Department.

B. Same patient, after single course of nitrogen mustard therapy. Note regression of atelectasis and shrinking of mediastinal nodes However, metastatic parenchymal deposits in left lung field have enlarged Patient experienced marked clinical improvement with gain in strength, weight, and appetite and relief of fever and dyspnea

(Courtesy *American Journal of Roentgenology and Radium Therapy*, 1949, 61, 633, Roswit, B , Kaplan, G.)

dyspnea, hemoptysis, fever, weakness, and other local and systemic symptoms Similar observations were made by 14 other investigative groups in a collected total of 254 cases (Roswit and Kaplan). Objective evidence of benefit, such as shrinking of parenchymal lesions, regression of atelectasis, and resorption of pleural fluid (Fig 6A, 6B) was observed infrequently. X-ray therapy may become possible after a preliminary course of nitrogen mustard. In patients with rapidly progressive compression of the superior vena cava, the palliative benefits with nitrogen mustard are often striking However, the remission is short-lived (averaging seven weeks), and should be followed promptly by roentgen therapy for more lasting benefit Roent-

gen therapy prolongs the period of remissions up to three months and occasionally up to a year.

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Complications. Nitrogen mustard is a powerful toxin and must be given ... of the possibility of local and systemic reaction ... and
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These may be controlled to some extent by employing sedation at the time of the injection and for several hours thereafter Chlorpromazine is useful in this connection. Leukopenia will be noted in about the third week in nearly all cases, and pancytopenia is inevitable after several courses There is no relationship between the severity of the leukopenia and the clinical result Cumulative and irreversible hypoplasia of the bone marrow may occur with repeated use of this agent. Penicillin and other antibiotics should be given when the leukocyte count reaches low levels

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mustard derivatives such as TEM (...), are not effective in treatment of leukemia and the malignant lymphomas, are not effective in patients with bronchogenic carcinoma

Radio-isotope Therapy

INTRACAVITARY TECHNIQUE

Indications Recurrent pleural effusion is often encountered in patients with bronchogenic carcinoma, and is rarely controlled by roentgen therapy alone. Repeated thoracentesis is attended by severe discomfort as well as by risk of infection and pneumothorax Karnofsky has reported some success through intrapleural injection of nitrogen mustard, but this approach has not been widely adopted

The mechanism for the effusion in this disease is still poorly understood Cancer seedings or tiny implants harbored in the pleural membrane may be responsible for an interference with the transfer of fluid across the pleural membrane In other instances lymphatic and venous channels may be blocked ... lymph nodes It would appear that in some ... range
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brane. This requirement has been effectively met by colloidal suspensions of radioactive materials which are introduced into the pleural cavity and flocculate on the pleural membrane A diffuse radiation pleuritis may thus be produced, with inhibition of fluid accumulation.

Radioactive Colloidal Gold (Au^{198}). Radioactive gold in colloidal suspension has become a useful palliative agent for control of this complication. Radioactive gold has a half-life of 2.7 days, with beta particle radiation (.96 MEV) and gamma radiation (0.4 MEV). The beta particles have a maximum penetration in tissue or water of 3.8 mm, but most of their energy is dissipated in the first millimeter. This agent is presently in use in many clinics in this country and abroad, and has proved worth while in about one-half to two-thirds of the cases thus treated Reports of favorable clinical experiences have come from Andrews, Root, Kerman and Bigelow, Kent and Moses, Knisely and Andrews; Maxfield; Storaasli; Bone, King and Friedell, Walton, and others.

The material is received in a cherry-red colloidal suspension, and a dose of 75 to 150 millicuries is promptly injected into the pleural cavity, after removal of most of the fluid A variety of injection techniques have been described, but the same principles apply to all maintenance of sterility, avoidance of radioactive contamination, protection of personnel from radiation hazard by speed, distance, lead shielding, and monitoring (film badges, survey meters, and dosimeters) The colloidal material is generally flocculated in large aggregates upon the pleural surface, and very little of it reaches the reticulo-endothelial system and blood-forming organs Severe impairment of blood elements has been rarely observed. Fibrous thickening of the pleura takes place, with extensive adhesions and pocketing of fluid after multiple injections Occasionally there is systemic discomfort such as anorexia, nausea, or vomiting following the intrapleural administration of this colloidal radiomaterial

Limitations of Radiogold Therapy A radiocolloid emitting only energetic beta particles would be more desirable for intrapleural therapy, because of the limitations and difficulties arising out of the penetrating gamma radiation from radiogold the gamma rays (0.4 MEV) create problems in personnel protection during the period of preparation and injection, the patient himself emits gamma radiation after the injection, hospitalization is required, and radiation sickness and leukopenia are encountered Since the half-life of radiogold is brief, most of the radiation is expended in about one week In addition, tracer studies reveal that the radiogold particles often remain in the pleural fluid for several days before actually depositing on the pleural surface.

Radioactive Colloidal Chromic Phosphate ($CrP^{32}O_4$) Radioactive chromic phosphate has been under investigation as a substitute for radiogold (Taylor, Andrews and Knisely, McCormick, *et al*). This agent has certain theoretical advantages over radiogold including: longer half-life—14.3 days;

more energetic beta particle with greater penetration into tissue, providing greater destructive action per disintegration, and pure beta particle emission with no gamma component, providing a reduction in radiation hazard to personnel and to the patient. This material can be safely injected in therapeutically useful dose levels. The pick-up by the bone marrow, liver, and spleen is clinically insignificant. There is no radiation sickness and no significant changes in the peripheral blood and bone marrow.

Radioactive chromic phosphate is employed in a colloidal suspension, with a particle size of about one micron. The optimum dose has not been established but it may range from 15 to 20 millicuries. Tracer studies reveal a prompt and almost complete flocculation of the material upon the pleural membrane within less than 24 hours.

Dose calculations have recently been completed by Yalow, providing the dose rates (rads per hour) at various depths in tissue from a thin source carrying one microcurie of P 32 per square centimeter. According to these data, it may be estimated that 20 millicuries of P 32 if homogeneously distributed to a pleural surface of 20,000 cm^2 will deliver a dose of approximately 6,000 reps at a depth of 0.05 mm. A dose of 1,500 reps will be delivered at 1 mm depth and 600 reps at 2 mm.

Jaffe, in evaluating his experience with colloidal chromic phosphate in fifty patients with pleural effusion concludes that this material has all the advantages of radiogold and none of its disadvantages, particularly in safety of handling. Our preliminary clinical experience supports this observation.

Yttrium 90 (half-life 2.54 days, 2.18 MEV beta) is undergoing preliminary clinical trial in several institutions for similar application to intracavitary therapy.

INTERSTITIAL TECHNIQUES

Metastatic bronchogenic cancer in the mediastinal lymph nodes frequently confronts the thoracic surgeon. Even in patients with 'silent' lesions, one out of four is found to have regional node involvement. *En bloc* nodal dissection of this area is virtually impossible. There would appear to be a field of usefulness for interstitial radiation therapy in such cases, either alone or in combination with external roentgen therapy.

Radon seeds have been implanted into mediastinal and hilar lymph nodes by some thoracic surgeons with the hope of retarding the malignant growth (Ariel, Head, Langston, and Avery). Recently, radioactive gold in the form of gold wire has been prepared for the same purpose. By this method there is always instantly available a supply of radioactive wire, seeds, or other linear sources, thus providing adjunct 400 KEV gamma radiation when inoperable primary tumors, nonresectable nodes, or other metastatic foci are to be dealt with during surgery (Myers, Colmery, and McLellan). Radioactive gold, in colloidal suspension, has been successfully employed intersti[tially] in prostatic cancer (Flocks, Wheeler, *et al.*), and may well be adapted

for use in bronchogenic carcinoma and other neoplasms. A gun has recently been perfected for implantation of radioactive gold grains into nonresectable tumors (Holt, Sinclair, and Smithers).

Radioactive colloidal chromic phosphate is under investigation in our laboratory for interstitial therapy of inoperable cancer from pulmonary and other primary sources Preliminary laboratory and clinical studies suggest that this agent may become still another worthwhile palliative adjunct, despite difficulties in achieving homogeneous distribution in tumor tissue and in determination of the optimum dose range (Mumma; McCormick, Mills, Jaffe, and Seid).

ENDOBRONCHIAL TECHNIQUES

Meneely, Auerbach, Woodcock, Korey and Hahn noted that when colloidal radiogold sol was administered by the tracheal route, the gold remained for many days in the lung parenchyma and did not gain access to the blood stream Cancerocidal doses of radiation could thus be delivered to any segment of the lung parenchyma via the appropriate bronchus. However, the gold colloid was drained very slowly by the regional lymphatics, taking from ten days to two weeks to reach concentration levels sufficient to permit adequate irradiation of the affected lymph nodes. Since the half-life of Gold 198 is only 2 7 days, it would thus appear to be less than ideal for this mode of therapy when the regional lymph nodes are involved Radiophosphorus, with its longer half-life (14.7 days) might be more effective when used in this manner. Limiting factors in the efficacy of this technique are the lack of intimate knowledge of the lymphatic drainage of the lungs, and the possibility of encountering lymphatics and lymph nodes completely blocked by tumor tissue By means of coating the gold particles with silver, Hahn facilitated the rapid transport of radiogold to regional lymph nodes following endobronchial instillation

INTRAVASCULAR METHODS

Muller and Rossier obtained selective fixation of radiogold in large particles within the lungs by injecting the solution by cardiac catheterization into a branch of the pulmonary artery corresponding to the involved portion of the lung In other experiments by the same investigators, Zinc 63 (half-life of 38 3 minutes) was also injected by placing the catheter in the pulmonary artery. Up to 150 millicuries were thus localized in several individuals. In some instances this was combined with intrapleural and interstitial injection of colloidal gold in connection with thoracic surgery.

TELECURIE THERAPY

The application of Cobalt 60 as a nuclear energy substitute for high energy X-ray machines in the treatment of deep-seated cancer has been widely

extended in the past two years. The advantages of this development have been described in the section on radical roentgen therapy This powerful source of gamma rays, equivalent to that produced by a 2 MV X-ray generator, makes it possible to deliver an effective tumor dose to an intrathoracic neoplasm without limitations of skin and systemic tolerance. Other radioactive materials such as Cesium 137 are undergoing intensive investigation for possible utilization in telecurie therapy

SURGICAL PALLIATIVE MEASURES

Palliative resectional surgery may be utilized to advantage for relief of the distressing symptoms resulting from necrosis of the tumor and secondary infection. Anaerobic suppuration of the lung produces putrid sputum, anorexia, fever, and weight loss. Limited resection is indicated for symptomatic relief, even though there is no possibility of long term survival. Intractable pain from metastatic involvement of the pleura, and profuse pulmonary hemorrhages are additional indications for palliative resection (See Chapter X for discussion of techniques)

Anesthesiology and neurosurgery have contributed much toward the relief of intractable pain Intercostal nerve block and neurectomy have been used with varying degrees of success Posterior rhizotomy with section of the involved nerve roots has proved a more effective procedure This method is precluded, however, where the lower cervical and upper thoracic nerve roots are involved. Posterior rhizotomy at this level would be followed by loss of position sense and impairment of useful function Cordotomy is also useful in painful areas of wider scope below the level of the seventh thoracic vertebra Unilateral prefrontal lobotomy may be considered in selected cases to relieve intransigent pain and its sequelae. After this procedure, the patient becomes relatively indifferent to pain and may even gain in appetite, strength, and weight. The necessity for large doses of narcotics often disappears promptly without significant withdrawal symptoms.

MEDICAL PALLIATIVE MEASURES

The duration of life in the lung cancer patient is sometimes unpredictable, and patients have lingered on for many months and even longer with widespread disease in the lung and in distant parts of the body During this period of slow progression, all attempts at supportive therapy are justifiable if there is any reasonable possibility of easing the distress of the patient The psychological effect on the patient's morale resulting from any apparent clinical improvement, no matter how slight, also must be considered. Symptomatic therapy of this type helps to ease the tension between patient and physician which inevitably develops in any chronic, progressive illness

Bronchopulmonary suppuration distal to the tumor produces symptoms which may dominate the clinical course of the lung cancer patient Many

of the symptoms associated with bronchogenic carcinoma are manifestations of this secondary infection. Cough, expectoration, malaise, fever, weight loss, and dyspnea may respond well to antibiotic treatment. Intensive therapy with penicillin, the sulfonamides, and the broad-range antibiotics often results in marked clinical improvement and, on occasion, renders the patient suitable for more specific treatment with radiation. *However, infection associated with central necrosis of the tumor is relatively unaffected by antibiotic drugs*

Oral and parenteral supportive therapy aimed at improving the nutritional status of the patient should be utilized in conjunction with the administration of antibiotics Cortisone is helpful in initiating improvement of well-being, appetite, weight, and strength These benefits are non-specific, representing suppression of the systemic manifestations of toxicity and inflammation Cortisone also appears to stimulate bone marrow activity at those periods when bone marrow depression makes the use of roentgen therapy and nitrogen mustard somewhat hazardous The nausea and vomiting produced by nitrogen mustard or radical radiation may be alleviated by the use of this agent A phenothiamine compound (chlorpromazine) has shown promise of intensifying and prolonging the action of narcotics and hypnotics *It is also effective in the management of the nausea and vomiting which may* attend roentgen therapy, and nitrogen mustard administration Other favorable effects include relief of pain, dyspnea, apprehension, and a sharp decrease in the need for narcotics.

Psychotherapy

The management of the patient with lung cancer presents many problems of a purely psychological nature The anxiety of the individual who suspects the diagnosis can often be allayed by referring to the condition in terms of its secondary manifestations such as 'abscess' or 'pneumonitis.' The similarity of the symptoms of lung cancer with other chronic pulmonary disorders makes this quite feasible. Discussions with patients or relatives regarding surgical intervention should be delayed until the case has been completely studied *Premature announcements with anticipation of surgical cure* may be responsible for complete collapse of morale if it is subsequently decided that the case is inoperable It is far better to state that investigative measures are necessary to determine which form of therapy is most suitable. In this manner there will be fewer shocking disappointments when other forms of treatment, such as radiation, have to be instituted

Post-operative patients require a great deal of encouragement to tide them over the period of convalescence Continuous thoracic pain may be a very disturbing sequel of surgery, and judicious administration of narcotics *is essential to avoid addiction* Exertional dyspnea and tachycardia are common complaints as the patient attempts resumption of normal activities, and

often lead to considerable apprehension. This can often be avoided by anticipatory explanations and precautionary instructions The post-pneumonectomy convalescent period may persist for several months, and the patient requires constant supervision and reassurance throughout the period

The care of patients with obvious metastases requires infinite patience and ingenuity Some are in fair general condition and live for one to two years before the terminal stage sets in It is in this group of patients that palliative therapy can be extremely useful both in relief of symptoms and in dispelling the despair and futility which permeates the sick room

Palliative therapeutic measures should be pursued with interest and enthusiasm Before instituting radiation or nitrogen mustard therapy, a clear explanation of the possible reactions, local and systemic, should be given to the patient and to the relatives who must participate in the management This allays the apprehension caused by untoward reactions and permits the continuation of treatment in a co-operative atmosphere

The patient with progressive bronchogenic carcinoma may develop psychiatric patterns of behavior which add considerably to the burdens of medical and nursing care. The intense anxiety associated with his condition makes it necessary for the patient to utilize some technique to relieve the stress A basic mechanism for tension release is the obliteration of inhibiting mechanisms and the relinquishment of adult behavior (Boyd) Child-like patterns of behavior may make their appearance—irritability, tantrums unreasonable demands, capriciousness, insistence on ritualistic routines of treatment, and intense desire for special attention from doctors, nurses, and family The management of the patient requires a sympathetic understanding of these phases of illness, which can often be avoided by establishing a secure patient-physician relationship early in the course of treatment

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